King County Medical Society Library

The Journal of Pediatrics

Vol. 13 December, 1938 No. 6

Original Communications

THE TREATMENT OF NEUROGENIC MEGACOLON WITH SELECTIVE DRUGS

Walter O. Klingman, M.D.
New York, N. Y.

A REVIEW of the literature on the subject of megacolon or dilatation of the colon leaves one without a clear understanding of both the pathology and etiology.[1] Since Hirschsprung's[2] original description of hypertrophy and dilatation of the colon in children, in 1888, many possible causes have been advanced, and a variety of therapeutic regimes have been tried.[3, 4] The more recent successful procedures in the treatment of megacolon have been those in which a better functioning of the bowel has resulted when part of the innervation of the colon has been surgically interrupted.

Originally the cause of megacolon was obscure, and it was known as congenital idiopathic dilatation of the colon. Congenital hypertrophy was thought to be the primary condition and spasm secondary, but both factors were present in all cases. Later neuromuscular unbalance was proposed as a primary cause, produced by a disturbed equilibrium between the two autonomic nervous systems supplying the gut and resulting in a paralysis of a segment of the colon. Fraser and Hunt[5] and others had felt that congenital idiopathic megacolon had a neuropathic cause resulting in a disturbance in the coordinating mechanism of the rectosigmoid and the anal sphincter. A theory originally expressed by Gaskell[6] and Sherrington[7] was later revived by Wade and Royle,[8] who felt that congenital dilatation of the colon was due to a postural tone being superimposed on the rectal mechanism which disturbed the coordination function of the sphincter. Fraser and Hunt were under the impression that the disturbed mechanism of the rectosigmoidal region was caused by a failure of the sphincter to relax.

From the Babies Hospital, New York City.

Bartle[9] in his excellent review of the literature which followed Hunter and Royle's work on the effects of sympathectomy for reduction of spasticity in the muscles of limbs paralyzed through a central or cortical lesion, proposed a new theory. He had studied the theories of the function of the sympathetic nerve supply of the bowel as propounded by Bayliss,[10] MacLeod,[11] Gaskell,[6] Langley,[12] and others.[13, 14, 15, 16] Bartle concluded that the neurogenic mechanism causing megacolon resembled the neurogenic mechanism responsible for the spastic extremities seen after central paralyses. He called attention to a case of Royle's where relief from an obstinate constipation of long standing had resulted, after the white ramus of the second lumbar had been cut.

Stimulated by the results obtained by Wade and Royle and the satisfactory results in two of Wade's patients, Judd and Adson proposed a new etiology for megacolon from their own investigations and operative experience. They stated that congenital megacolon and megacolon acquired in early life without obvious mechanical obstruction are due to hyperactivity of the sympathetic innervation of the rectum. This theory was based upon the dual innervation of the rectum and anus with parasympathetic and sympathetic fibers. The motor impulses to the longitudinal muscle fibers of the rectum were known to be transmitted by the parasympathetics and the motor impulses to the circular muscles of the rectum by the sympathetics, partially arising from the lumbar rami communicantes passing down through the sympathetic trunks, the hypogastric and pelvic plexuses. Conversely, the inhibitory impulses to the longitudinal muscle fibers were supplied by the sympathetics, the inhibitory impulses to the circular fibers being supplied by the parasympathetics. It was not possible for them to deduce whether the hyperactivity of the sympathetics postulated in cases of megacolon was due to an irritating lesion of the ganglia of the postganglionic or the preganglionic fibers or was of central origin; but they favored the latter view. Therefore, they proposed and performed lumbar sympathetic ganglionectomy and ramisectomy for congenital idiopathic dilatation of the colon. They felt that the resulting improved colon emptying was not necessarily due to division of the white ramus or to removal of the lumbar ganglia but to a thorough interruption of the sympathetic chain below the last white ramus, preganglionic fiber to the ganglia. The division of the lumbar sympathetic chain diminished the sympathetic stimuli to the circular muscles of the rectum and, when symptoms of obstruction and toxicosis developed, division of the lumbar sympathetic trunks should be considered.[17] Their results were very encouraging.

Learmonth, in reviewing operations on the sympathetic nerves of the terminal portion of the bowel and of the bladder, stated later that a surgical procedure confined to the lumbar sympathetic trunks and their branches does not interrupt all the sympathetic fibers passing to the terminal part of the bowel.[18] Judd and Adson had felt, however, that

interruption of the sympathetic influence, as achieved by their operation, resulted in a better functional balance between sympathetic and parasympathetic systems. Learmonth preferred to interpret the operative outcome as a better integration of the different functions of the nervous system.

From Judd and Adson's report it was assumed that there was a type of megacolon which was due to autonomic nervous system unbalance in the nature of hyperactivity of the sympathetic system resulting in tonic spasm of the sphincter or rectosigmoidal apparatus. Fraser and Hunt had already suggested that a similar condition might be due to lack of inhibition of the sphincter. Prompted by these studies, we considered attacking the problem on the premise that some types of megacolon might be due to an inability of the sphincter or rectosigmoidal apparatus to be properly inhibited or that the unbalance resulted from faulty inhibition.

In the light of the newer knowledge of the physiology of nerve control of the rectosigmoid, a rational therapeutic approach with properly selected drugs has been attempted. Atropine has been used for years, but the rather undesirable toxic atropine effects have discouraged its use. Furthermore, lack of classification of the types of neurogenic disturbance has hindered a solution of the problem from the pharmacodynamic standpoint, and until these types of megacolon could be distinguished clinically, selective drug therapy was not possible.[19-21]

Clinically, idiopathic or acquired megacolon, we believe, falls into one of two groups, excluding mechanical obstruction of the colon. First, there is a group called rectosigmoidal achalasia, in which one finds a failure of the rectosigmoidal apparatus to relax. Secondly, there is a group in which one finds a failure of the motor function of the parasympathetic system to act effectively above the rectosigmoidal region. Rectosigmoidal achalasia may arise from two causes: one due to overactivity of the sympathetic system resulting in spasm of the rectosigmoidal apparatus, and the other due to failure of the parasympathetic system to properly inhibit the rectosigmoidal apparatus.

A series of seven cases was studied. All of these cases were being considered for surgical treatment. At first no definite plan of medication was carried out, but we tried one drug and if that did not work we tried another. Benzedrine sulfate, ephedrine sulfate, and atropine sulfate were all tried. Atropine had been effective for intervals in the first cases studied but the by-effects were so annoying that it had to be discontinued. In view of the satisfactory response to atropine sulfate, despite the unpleasant toxic effects, we felt that the parasympathetic system undoubtedly played a considerable part in the production of disturbed neuromuscular function. Therefore, in searching for a selective drug, it seemed advisable to choose one which would act exclusively on the parasympathetics. Just how atropine or one of its derivatives

or a drug acting exclusively as a paralysant of the parasympathetics becomes effective in establishing better bowel function in megacolon is difficult to explain. One working hypothesis is that with overaction of the parasympathetics retention in the colon occurs from inability of the longitudinal muscle fibers to expel the feces without help of the circular fibers, which in neurogenic megacolon are too completely relaxed. A parasympathetic paralysant would lessen this inhibiting effect and one then might get some circular muscle fiber action. Gaskell and Sherrington suggested that megacolon was a disturbance of postural tone of the gut. With a disturbance of this kind one might expect some interferences in the coordinating function of the rectal sphincter mechanism. A parasympathetic paralysant in that event would help the motility of the colon even if the posture of the gut were not helped.

Still another thought in explanation of the action of a parasympathetic paralysant is given by Loewi,[22] who says that a drug like atropine inhibits the action of the parasympathetic nervous system not by paralyzing, as has been supposed, but by stopping or preventing the action of acetylcholine in or near the reacting cell. He also states that when a balance obtains between cholinergic and adrenergic substances, atropine, by removing the cholinergic factor, acts as a synergist to the adrenergic factor. Myerson's experiments would also lead one to accept this view.[23] In particular reference to the gastrointestinal tract, the tonus of the rectosigmoidal apparatus may be diminished by adrenergic action, following administration of a parasympathetic paralysant.

Yet another explanation may come from the effect that a parasympathetic paralysant may have when it acts by inhibiting the liberation of acetylcholine. Aside from being liberated in very small quantities ordinarily at the terminations of the parasympathetics, acetylcholine is also present in small quantities at the terminations of the sympathetic fibers at the junction of the preganglionic and postganglionic fibers. A drug reducing the liberation of acetylcholine at this junction might sufficiently reduce the overactivity of the sympathetic innervation and lead to a better balance (Fig. 1).

In some respects the use of a parasympathetic paralysant is almost paradoxical, and one is forced to accept it on the grounds that it is effective, the means by which it acts being as yet unexplained. Rather contradictory findings from atropine are being observed elsewhere by investigators, especially where an unbalance exists or is artificially produced by other drugs.

Whatever the explanation may be, drugs acting exclusively on the parasympathetics as paralysers are beneficial in establishing better emptying of the bowel in certain cases of megacolon.

The drug of choice to inhibit liberation of acetylcholine should be atropine but, as already mentioned, its highly toxic effects contraindicate

its administration. In a search, therefore, for a less toxic atropine-like compound, syntropan was selected because of its inhibiting effect, similar to atropine on the reacting cells, at the parasympathetic nerve endings.

Syntropan is the ester of 3- diethylamino-2, 2- dimethyl-1 propanol and tropic acid and is marketed under the name of syntropan (Roche). It was selected because it controls tonus without interfering with the peristaltic reflex. It also has a much greater safety ratio than atropine sulfate, the toxic dose being more than twice that of atropine. Likewise, its administration is not accompanied by the disagreeable effects on circulation, the pupil, and the glandular secretions. Its effect on the colon is also much greater than that of atropine and it has no atropine-like action on the small intestine. The effective dose of syntropan is also much more easily reached without appearance of any toxic symptoms, which is not true of atropine. In all cases it was given by mouth.

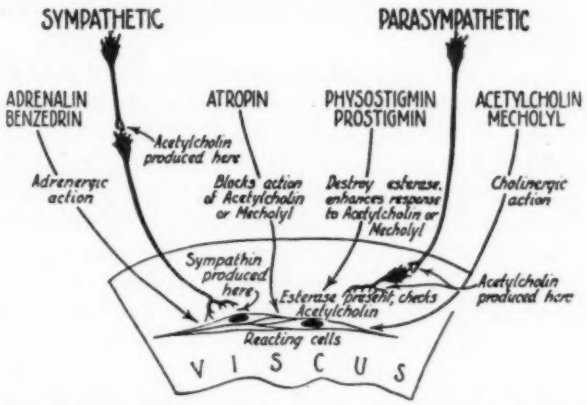

Fig. 1.—Myerson's schematic illustration of the points of action of various adrenergic and cholinergic drugs. (J. A. M. A. 110: 102, 1938.)

All of the cases treated were first tried with syntropan. Of the seven cases treated, five of them responded to such treatment. The exceptions are mentioned in detail later. The patients ranged in age from 8 months to 14 years. All of them had preliminary barium studies to demonstrate the existence of megacolon (see x-ray plates).

The result of treatment has been excellent. The case reports below show a satisfactory bowel function which has continued throughout the follow-up period in all suitable cases, with no indications of loss of effectiveness of the drug. On the contrary, some of the patients are doing very well on reduced dosages, and two patients are no longer taking syntropan and have normal bowel function.

In the group of rectosigmoidal achalasia, a single case is presented, Case 1, in which we felt that the condition was due to motor hyperactivity of the sympathetics. There was in this instance a similar fail-

ure of the rectosigmoidal apparatus to relax, but the condition did not respond to syntropan therapy. The dosage was increased as high as we felt it was safe to do so, being uncertain when toxic central symptoms might appear. Because of lack of a safe and practical drug for reducing sympathetic function, we thought it right to advise a presacral nerve resection and ganglionectomy on this patient. Perhaps we were too hasty in abandoning ephedrine or benzedrine sulfate drug therapy in the treatment. Ergotamine tartrate was not tried because of the impractical feature of giving it subcutaneously, as its effectiveness by mouth is rather dubious. It is quite possible that this is the type of case (hyperactivity of the sympathetics) that ultimately one would select for surgical treatment, whereas the other types may be treated medically. The other cases in the group of rectosigmoidal achalasia were all in patients who showed a failure of the rectosigmoidal apparatus to relax because of lack of proper inhibitory function of the parasympathetic system.

In a third type, showing no disturbance of the function of the rectosigmoidal apparatus by roentgenographic studies but where there was an obvious weakness in the expulsive musculature of the colon above the rectosigmoidal region, we felt that the disturbance was due to failure of the parasympathetics to initiate or maintain the expulsive mechanism (longitudinal muscle fibers) of the colon. The drug of selection here should be one which again acts exclusively on the parasympathetic system. Physostigmine would be the drug of choice, were it not too toxic. A physostigmine-like preparation was selected, prostigmine, which supposedly intensifies the action of acetylcholine at the terminations of the parasympathetic fibers. Acetylcholine is normally rapidly destroyed in the tissues by an esterase. Because physostigmine and prostigmine utilize in their own hydrolytic destruction much of the esterase that would otherwise be left free to destroy the minute amounts of acetylcholine constantly being liberated by the parasympathetics, there is a diversion of the esterase from the acetylcholine which allows it to accumulate in larger quantities and thus produce greater pharmacologic effects.[22] The single patient treated has made a very satisfactory response and has continued good bowel function on a gradually diminishing dosage of medication. The medication was given by mouth.

So far, we have encountered no cases where there has been overactivity of the sympathetic innervation of the colon above the rectosigmoidal apparatus. It is our impression, however, that this condition does exist and that there is a group of disturbances due to faulty balance of the autonomic innervation of the colon above the rectosigmoidal apparatus in which either parasympathetic or sympathetic elements are the offenders. It is possible that the classical types of atonic and spastic

constipation belong to this group. Studies on these latter conditions are now being pursued with hope of determining their etiology from the standpoint of the neuromuscular mechanism.

We propose the following classification of the neurogenic disturbance resulting in megacolon with constipation, based on the reported experiences in the literature and on our own clinical studies:

1. Cases of rectosigmoidal achalasia: (a) Those caused by motor hyperactivity of the sympathetic innervation to the rectosigmoidal apparatus (cases which are not influenced by any known or tried medications); (b) those caused by ineffective inhibitory function of the parasympathetic innervation to the rectosigmoidal apparatus (cases which respond to parasympathetic paralysants).

2. Cases of deficient motor function of the innervation of the colon above the rectosigmoidal apparatus: (a) Those caused by deficient parasympathetic motor function (cases which respond to parasympathetic stimulants); (b) those caused by deficient sympathetic motor function.

Clinically, the two types of rectosigmoidal achalasia cannot be distinguished except after trial of appropriate drug therapy, as outlined above, but by barium enema study it is frequently possible to demonstrate whether or not there is rectosigmoidal spasm with or without delayed emptying of the colon. In cases of rectosigmoidal achalasia there is marked delay in emptying, whereas in the cases where there is deficient motor function on the part of the parasympathetics of the colon above the rectosigmoidal apparatus there is good emptying of the lower colon but retention of the barium in the upper colon.

Based on the above classification, we propose a selective form of treatment for each of the conditions classified. When x-ray interpretation makes it possible to establish that the rectosigmoidal apparatus is functioning, one should try prostigmine. If the rectosigmoidal apparatus is not functioning one tries first benzedrine sulfate and then syntropan. If there is no response to either of the latter drugs, we propose continuing the present surgical treatment of lumbar ganglionectomy and presacral resection, until more satisfactory selective drug action can be found.

COMMENT

In a review of the literature on megacolon with constipation, whether congenital or acquired, it is evident that the theories postulating a neurogenic origin of the condition have gained strong support from accumulated clinical and experimental evidence. This support was largely given by the development of a form of treatment consisting of lumbar sympathectomy and ganglionectomy. The recent advances in pharmacology and also in the studies of the autonomic nervous system have opened new avenues for attacking the problem of megacolon with

drugs of the cholinergic and anticholinergic type. One cannot at this time be too dogmatic as to the anatomic or pharmacologic theories supporting the explanations given for the results obtained in the cases mentioned in this paper. However, the clinical results of effective bowel functioning must be considered as a strong argument in favor of the theories expressed. Many factors must be taken into consideration in the treatment of constipation with megacolon. Change of environment by placing patients under hospital routine and type of diet might be stressed by some as a deciding factor in establishing good bowel functioning. However, objection may be raised against this as being a factor in that most of the cases were observed in the hospital for a sufficiently long period without acquisition of good bowel function before treatment was started. One patient had been in the hospital for two observation periods of several weeks with no beneficial results.

Several points of interest should be mentioned. All of the cases studied showed the same symptoms, namely, severe constipation, usually bowel movement by enema only, abdominal distention, visible peristalsis, muscle atrophy of the abdominal wall, toxic symptoms, spastic or hypertonic anal sphincter, and x-ray findings of megacolon after barium enema.

After treatment, the majority of the cases did well on reduced dosage of medication, two patients no longer requiring any medication. It is quite possible that the drugs used have been beneficial in setting up acquired reflexes which are constantly at work regulating the bowel actions.

Neither surgical nor medical treatment sheds any light on the etiology of megacolon other than to demonstrate that it probably arises from an autonomic nervous system unbalance. Most probably the dilatation and hypertrophy of the colon, which constitute the characteristic morphology, are compensatory changes that arise in an attempt to remove the fecal content of the sigmoid.

SUMMARY

1. An attempt has been made to attack the problem of megacolon on the basis of neurogenic unbalance.

2. A classification of neurogenic disturbances resulting in megacolon with constipation has been proposed on the basis of barium enema study and a trial of appropriate drug therapy.

3. Surgical treatment of neurogenic megacolon is advisable for those cases where there is extreme overactivity of the sympathetic innervation to the rectosigmoidal apparatus.

4. Selective drug therapy has proved effective where neurogenic unbalance exists because of faulty inhibitory or motor function of the parasympathetic system.

ABSTRACTS OF CASES STUDIED

1. Cases of rectosigmoidal achalasia.

a. Those caused by motor hyperactivity of the sympathetic innervation to the rectosigmoidal apparatus.

CASE 1.—M. D., Babies Hospital, No. 525528, male, aged 10 years, was admitted Aug. 21, 1937, and discharged Dec. 5, 1937.

At the age of 2 or 3 weeks the mother noted that the child had become very constipated and rarely, if ever, had a normal bowel movement. He had been given an enema almost daily since then and for two months before admission, received along with various dietary measures directed at control of constipation, one tablespoonful of mineral oil each day and an oil enema every other night. His appetite was never good. His abdomen had always been prominent and changed its shape

Fig. 2.—Case 1. Barium enema study made before operation. A case of hyperactivity of sympathetic innervation to rectosigmoidal junction resulting in tonic spasm of that region.

frequently. Five months before admission, at the age of 10, he had an attack of extreme constipation, with vomiting and abdominal distention, which required an operation for acute intestinal obstruction at the Hackensack Hospital. The type of operation performed was not determined.

The patient was started on syntropan by mouth and was given gradually increasing doses, receiving up to 165 mg. per day, but without any effect (Fig. 2).

He was operated on Nov. 13, 1937, having a presacral neurectomy done. He had his first bowel movement spontaneously on the sixth day after the operation. Six months later he was having daily bowel movements without help of any kind.

b. Those caused by lack of proper inhibitory function of the parasympathetic innervation of the rectosigmoidal apparatus.

CASE 2.—A. A., Babies Hospital, No. 403707, male, aged 27 months, was first admitted Dec. 29, 1933, at the age of 2 years and 3 months. He was discharged Jan.

19, 1934. He was admitted the second time on Jan. 28, 1937, at the age of 5 years and 4 months; he was discharged March 21, 1937.

The child had been constipated since birth; the bowels had never moved without either an enema or a cathartic and often even with these measures the patient would go a week without a satisfactory spontaneous movement. The stools then were unusually small and ribbonlike. The abdomen was always large. Vomiting would occur about every two weeks. His appetite had always been good. Examination showed a distended, protuberant abdomen and the transverse, descending, and sigmoidal colon were palpated. The internal sphincter was quite spastic.

Barium enema at the time the patient was 27 months old (Fig. 3) showed a greatly elongated and dilated sigmoid and colon; the rectum remained undilated. After twenty-two hours, a large amount of retention was present in the dilated and elongated sigmoid. The patient was then discharged as being too young to be operated upon. He was readmitted to the hospital on Jan. 28, 1937. He had been receiving a milk and molasses enema each evening for eighteen months after the time of his first discharge, and then a simple enema almost every night, but he never had a stool unaided by enema.

The patient was tried on benzedrine sulfate with no effect, receiving up to 10 mg. a day. Then he was placed on syntropan starting with 5 mg. by mouth, three times a day and gradually increasing up to 150 mg. a day, when satisfactory bowel movements were established. After his discharge from the hospital the dosage was gradually reduced to 50 mg. in the morning and 25 mg. in the afternoon, and at the present time he is maintained on 25 mg. once daily.

Barium enema after syntropan administration disclosed that the colon still was markedly dilated; it showed marked improvement in the emptying time, and the colon was free from barium after five hours.

CASE 3.—J. F., Babies Hospital, No. 517616, male, aged 8 months, was admitted June 4, 1937, and was discharged June 18, 1937.

There was a history of no spontaneous bowel movements since birth. After birth the abdomen was very distended and there was a very tight anal sphincter. A daily enema was given since birth, laxatives being ineffectual. If enemas were not given daily at first, distention would always result. Vomiting had occasionally been present. Rectal examination showed a constricted ring at the upper rectum. The abdomen was moderately distended and the sigmoid was easily outlined.

Barium enema showed megacolon of moderate degree (Fig. 4). Retention of the barium was still present after forty-eight hours.

The patient was started on syntropan, 5 mg. three times a day and the dosage was increased gradually to 18 mg. three times a day, when regular bowel function of three or four stools was established. Then the bowel movements became so frequent that the medication was reduced and then discontinued. Normal bowel function has continued up to this time.

CASE 4.—P. K., Babies Hospital, No. 510468, female, aged 8 years, was admitted Feb. 15, 1937, and discharged March 6, 1937.

There was a history of constipation since infancy. Vomiting had frequently occurred in the neonatal period and a pylorospasm was suspected. Constipation was so severe that enemas and mineral oil were used very frequently. She was subject to attacks of abdominal pain. The stools were ribbonlike. Barium enema showed an enormous increase in caliber and length of colon, the rectum being of normal size (Fig. 5). There was a constriction above the rectosigmoidal junction at the approximate level of the fourth lumbar vertebra.

She was started on benzedrine sulfate, receiving up to 17 mg. per day with no effect. Then she was placed on syntropan, and bowel function was established on

a dosage of 25 mg. in the morning, 12.5 mg. at noon, and 25 mg. in the afternoon. Bowel function was maintained on an average dose of 50 mg. per day. Follow-up barium enema showed a dilated colon as before, but there was a markedly improved emptying time.

Fig. 3. Fig. 4.

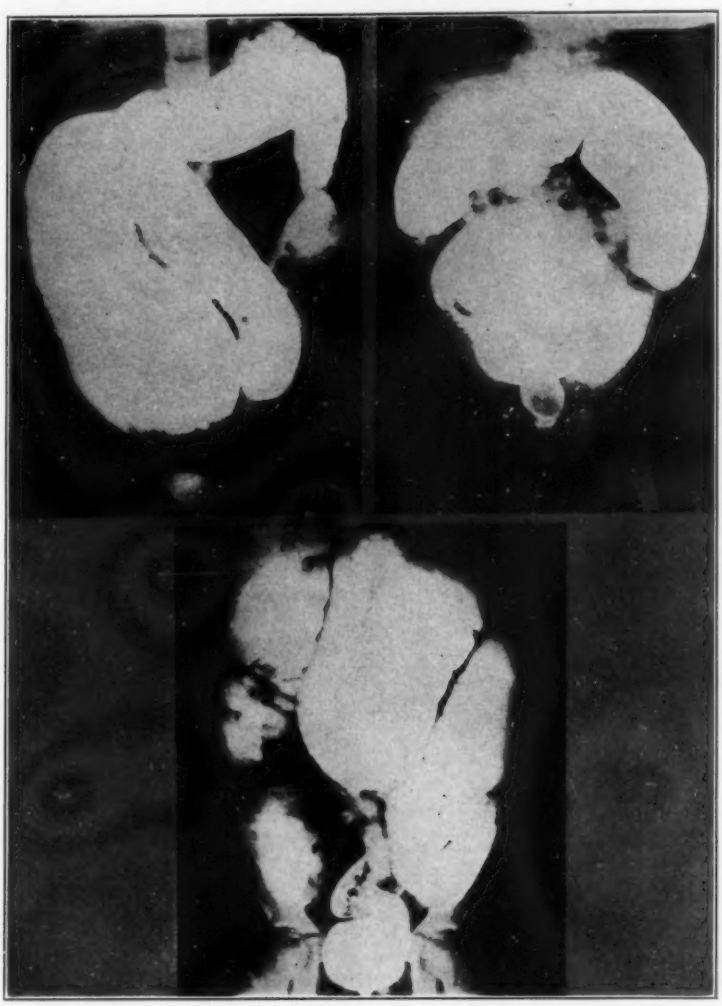

Fig. 5.

Fig. 3.—Case 2. Barium enema study made before treatment. A case of faulty inhibitory function of parasympathetic innervation to the rectosigmoidal region.

Fig. 4.—Case 3. Barium enema study made before treatment. A case of faulty inhibitory function of parasympathetic innervation to the rectosigmoidal region.

Fig. 5.—Case 4. Barium enema study made before treatment. A case of faulty inhibitory function of parasympathetic innervation to the rectosigmoidal region.

CASE 5.—M. W., Babies Hospital, No. 517596, male, aged 5 years, was admitted May 27, 1937, and discharged June 18, 1937.

The patient had been very constipated since birth and had never had a spontaneous bowel movement. Diets and medications had been tried and enemas were eventually relied upon. The stool had always been of small caliber. On one occasion he had been admitted to a hospital because of obstruction but was not operated upon. He had been receiving five tablets three times a day of 1/1000 grain of atropine and 5 ounces of olive oil per rectum each night, before coming to the hospital. Examination revealed a protuberant abdomen and easily palpated sigmoid and colon. It proved impossible to pass a proctoscope more than 5 cm. beyond the anal ring.

Barium enema revealed a marked elongation and dilatation of the colon above the rectosigmoidal region, extending for a short distance in the terminal portion of the sigmoid and giving the appearance of a rectal stenosis (Fig. 6).

Fig. 6. Fig. 7.

Fig. 6.—Case 5. Barium enema study made before treatment was started. A case of faulty inhibitory function of the parasympathetic innervation to the rectosigmoidal region. The region of constriction here has the appearance of a stenosis.

Fig. 7.—Case 5. Barium enema study made after successful treatments with syntropan, showing improved emptying after the first defecation within an hour after barium enema was given.

He was started on syntropan by mouth, and at a dosage of 25 mg. three times a day regular bowel function was established and has persisted. A follow-up barium enema showed no significant changes in the outline of the bowel but good emptying of the colon (Fig. 7).

CASE 6.—F. D., outpatient, female, aged 14 years.

There was a history of severe constipation since birth, with no spontaneous bowel movements. Enema had been relied upon entirely at first with a trial of most of the cathartics and oils from time to time. Eventually a routine was established for an enema every other day. On some rare occasions, by taking cathartics, she had successful daily emptying for as long as four or five days.

Barium enema showed an enormously dilated sigmoid and descending colon with normal rectum (Fig. 8). The rectosigmoidal junction was strictureliké, and there was marked delay in emptying.

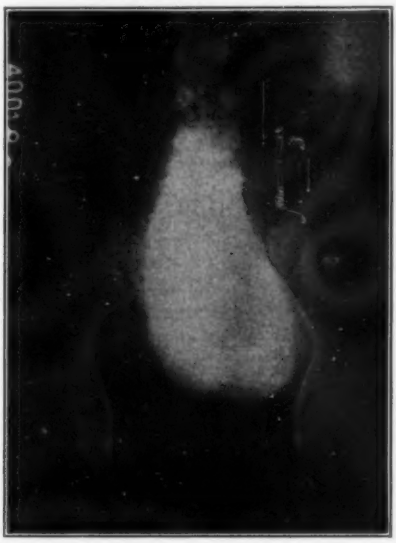

Fig. 8.—Case 6. Barium enema study made before treatment was started. A case of faulty inhibitory function of the parasympathetic innervation to the rectosigmoidal region.

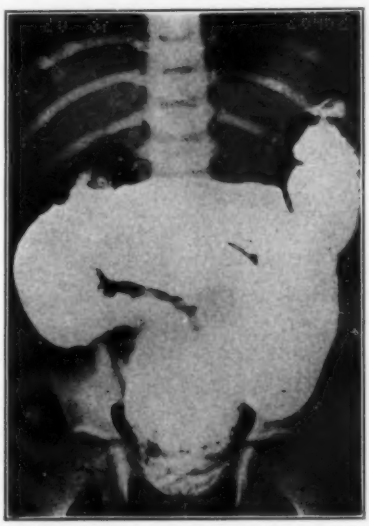

Fig. 9.—Case 7. Barium enema study made after treatment with prostigmine. A case of deficient parasympathetic motor function of the colon above the rectosigmoidal region.

The patient was placed on syntropan and became regulated as to bowel movements after reaching a dosage of 50 mg., three times a day. Barium enema taken three months after normal bowel function was established still showed the colon to be markedly enlarged but there was a distinct improvement in the emptying.

2. Case of deficient motor function of the parasympathetic innervation of the colon above the rectosigmoidal apparatus.

CASE 7.—C. Q., Babies Hospital, No. 517662, male, aged 3 years, was admitted June 21, 1937, and discharged July 20, 1937.

The patient had always been severely constipated and had seen many doctors from the age of 1 month on. Many laxatives and cathartics had been tried; finally soapsuds enemas and olive oil enemas were used. Spontaneous movements sometimes occurred on a day after enema and when Ex-lax had been given. The stool was always of large caliber and never of pencil form. Barium enema showed an elongated sigmoid, with good evacuation of the barium. The patient was started on prostigmine 5 mg. three times a day and increased by 2 mg. every two days. He became regular in his bowel movements after a dosage of 12 mg. three times a day was reached.

Follow-up barium enema one month later showed no appreciable change in the size of the transverse diameter of the large bowel and no evidence of delay or obstruction. The redundant sigmoid was present as before. A second follow-up barium enema four months after treatment was started (Fig. 9) showed elongated sigmoid as before and a satisfactory emptying of the colon, but no evidence of dilatation of the colon. The patient has been having two or three evacuations a day since leaving the hospital. The mother gradually reduced the dosage of prostigmine and when last seen she had discontinued it entirely and was giving small amounts of mineral oil only.

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OBSERVATIONS ON CONGENITAL MEGACOLON

GEZA DE TAKATS, M.D., AND ALFRED D. BIGGS, M.D.
CHICAGO, ILL.

CONGENITAL megacolon, frequently referred to as Hirschsprung's disease, had been described by more than twenty authors before Hirschsprung's communication in 1886.[1] Nevertheless, he has popularized this clinical entity and has given a description of the disease to which little can be added today. Because of the rarity of the condition, reports of single or a few cases have appeared from time to time and have been ably summarized in collective reviews by Finney[2] in 1908, by Neugebauer[3] in 1913, by Fowler, Davidson, and Mellon[4] in 1922, and by Ask-Upmark[5] in 1930. A recent monograph of Pässler[34] brought the bibliography up to date.

In 30,000 autopsies in the London Hospital for Sick Children, Fenwick could find only three cases, an incidence of 1:10,000.[1] At a later date, R. C. Lightwood found that one in every 2,620 patients at the same institution suffered from megacolon.[6] In a general hospital, Walton found an incidence of four to 131,000. We found nine cases at St. Luke's Hospital in the years between 1931 and 1937, during which time 79,035 admissions occurred; this would give an incidence of 1:9000. Uniformly, the prevalence of males over females has been stressed, in a ratio of 3:1 to 5:1. Megacolon may be present at delivery; in fact it has been reported in a 7-month-old fetus (Von Ammon, 1842); but of 223 cases, reported by Patel, seventy-three were in adults. Corbin reports 200 cases from the Argentine among adults who have come under his personal supervision.[7] Whether these cases may be truly regarded as megacolon or simply are due to long sigmoid loops with atonic constipation is debatable. Our fifth, eighth, and ninth cases were in adults lacking a history of constipation in childhood.

Many theories have been advanced as to the causes of this disease, and we have summarized the most important ones in Table I. It is quite likely that several factors may contribute to this intractable hypertrophy and dilatation of the colon and that the etiology may vary. It is obviously important to study the etiology of the disease if we are to evolve logical and satisfactory methods of management. For this reason some clinical and experimental data which have a bearing on etiology must be discussed.

THE MECHANICAL FACTOR IN CONGENITAL MEGACOLON

While the original definition given by Hirschsprung really excludes all patients with a demonstrable rectal obstruction, nevertheless, cases

From the Department of Surgery, University of Illinois, College of Medicine and St. Luke's Hospital. Presented before the Chicago Pediatric Society, March 15, 1938.

TABLE I

POSSIBLE CAUSES OF MEGACOLON

TABULATION OF THE THEORIES ADVANCED	
A. Congenital Anomalies	*C. Other Causes*
Dilatation and hypertrophy (Hirschsprung)	Lymphangiectasis resulting in gigantism (Finney)
Dilatation and hypertrophy (Mya)	Chronic colitis (Walker and Griffith)
Hypertrophy, secondary dilatation (Fenwick)	Diastasis of rectus muscles (Levi)
Congenital defect (Bailey)	Atony associated with wasting disease (Griffith)
B. Mechanical Obstruction	*D. Neuromuscular Dysfunction*
Too long mesosigmoid (Barth)	Neuromuscular segmental defect (Formad, Hawkins)
Too long sigmoid loop (Marfan)	Segmental paralysis (Pennato)
Obstruction in terminal bowel (Treves, V. David)	Defective muscular tone (Murray)
Obstruction at Houston's valves (Perthes)	Lesion of sympathetic nerves (Bing)
Distention of colon by meconium (Wilkie)	Reflex spasm of sphincters (Fenwick)
	Failure of coordination (W. J. Mayo)
	Achalasia of terminal bowel (Hurst)
	Delay of inhibition (Fraser)
	Increased plastic tone (Royle)

presented by Treves,[8] Vernon David,[9] and Brenneman[10] amply demonstrate the importance of bearing an anorectal stricture in mind. One of our own patients (Case 2) had a diaphragmatic type of stricture one inch above the anocutaneous zone. In spite of daily dilatations, which finally resulted in a complete disappearance of the stricture, the megacolon progressed. Case 6 had an imperforate anus, which ultimately resulted in fecal incontinence.* In Brenneman's two cases, which came to autopsy after two weeks of dilatation, no trace of any diaphragm could be found at post mortem, nor could Dr. C. J. de Bere find any stricture by proctoscopic examinations in our patient a few weeks after birth. One wonders whether or not a tight sphincter might occasionally give the impression of a partial atresia and also whether in the presence of a true atresia the megacolon might not be due to a loss of reflexes from the anal canal.

A long sigmoid loop or a long mesentery of the sigmoid have been accused of being the causes of megacolon. True enough, some patients suffering from megacolon have abnormally long sigmoid loops; this was found also in six of our patients. But it must be stated that: (1) the elongation of the loop may be the result and not the cause of colonic stasis; (2) not all cases of megacolon have long sigmoid loops—Case 3 had a very short, spastic sigmoid loop; (3) there are many cases of dolichocolon (long sigmoid loop) seen in the x-ray department which have never given rise to colonic dilatation and hypertrophy or constipation.

The possibility of kinks and valvular mechanisms, especially at the sigmoid flexure, has been emphasized ever since the careful study of a colostomized patient by Perthes[11] in 1905. He found that while an

*This was true of a recently observed, tenth case, which is not reported here.

enema could easily pass the Houston valves from the rectum through the colostomy, nothing would pass in the opposite direction. Following division of the folds in the mucosa, marked improvement resulted. It is probable that these valvular mechanisms do play a role, but only after the colonic stasis and distention have become established. Hurst,[6] whose views on megacolon will be quoted repeatedly, believes that the pelvirectal sphincter of O'Beirne is a myth; but he does state that the three Houston valves, which are normally easily overcome by the gastrocolic reflex, may produce mechanical obstruction in the previously distended and kinked bowel.

The occurrence of a volvulus of the long and distended sigmoid loop has been reported; Case 2 showed such a partial volvulus on one admission, but high colonic enemas relieved it. Case 1 had a huge fecal impaction in a long sigmoid loop, which was resected.

Thus, it may be said that while mechanical factors may play an important role in the production of symptoms, and especially as secondary complications, there exists a group of cases in which the underlying, primary mechanism must be elsewhere.

CONGENITAL ANOMALIES

That megacolon is present at birth and sometimes in the fetus has been repeatedly reported. Most case histories, if carefully analyzed, reveal the fact that distention and intractable constipation were obvious in the first weeks after birth. Six of our cases give such a history. Other congenital anomalies, such as imperforate anus, pyloric stenosis, rectovaginal fistula, or bicornuate uterus, may be present. Case 6 had a transposition of the heart, lungs, and liver to the opposite side. The anomaly producing the disease was said by Hirschsprung, Mya, Fenwick, and Bailey to be a congenital dilatation and hypertrophy, but this, of course, does not explain the mechanism of its production. Other causes, such as lymphangiectasis resulting in gigantism, chronic colitis, diastasis or absence of the rectus muscles, and atony of the bowel, have been suggested but have not been generally accepted.

NEUROMUSCULAR DEFECT

That a segment of the colon, mostly the sigmoid, might be paralyzed or have a defective muscular tone has been advanced early among the theories of megacolon. Fenwick spoke of a spasm of the anal sphincter and hypertrophy of the colon proximal to the obstruction. Lately much interest has been focused on the role of the visceral motor mechanism in the production of megacolon. Hurst,[6] one of the most experienced clinicians in this field, who has seen thirty-two cases and studied them with great care, feels that megacolon is due to an absence of relaxation of the sphincter ani, when the normal colonic peristalsis reaches the rectum. This achalasia, which is analogous to the so-called cardiospasm,

is not a rectal spasm, nor is there an overactivity of the sympathetic nervous system, but rather a diminished tonus of the sacral, parasympathetic outflow. Inflammatory reactions around the anus may produce such achalasia by degeneration of the Auerbach plexus. Thus the stimulus for the act of defecation is poorly transmitted (Brown[12]).

The theory of Hurst, which has been expressed by others as failure of coordination, delay of inhibition or neuromuscular dysfunction, has much experimental and clinical support. In the first place, it is obvious to anyone who has had the opportunity to study any of these children that the colon of the patient, in spite of its dilatation, is not paralyzed. In fact, vigorous and painful peristaltic movements are always seen, especially when the colon is hypertrophic. The intestinal obstruction of these patients has all the earmarks of a mechanical obstruction, and yet at autopsy no such obstruction can be found. The bowel then must be contracting, either against the closed sphincter, which fails to relax, or against a valvular obstruction or kink. When the sphincter is dilated manually or by systematic use of conic bougies, which are passed every morning and kept in for half an hour, improvement frequently results.[6]

The last theory, which was proposed by Wade and Royle,[13] postulates an increased postural or plastic tone of the bowel which is mediated by the sympathetic nervous system, just as in striated muscle. This principle, which was equally adapted to the treatment of spastic paralysis, has since been definitely shown to be incorrect; nevertheless, it opened a vast field for the surgery of the sympathetic nervous system. While the theory of the operation is not tenable, the results were surprising.

THE PERVERTED PHYSIOLOGY OF MEGACOLON

If, as emphasized in the above analysis of hypotheses, the lack of coordination between proximal and distal parts of the colon seems to be the most likely cause of the congenital primary megacolon, it seems profitable to summarize briefly the knowledge concerning the innervation of the distal colon. Peristalsis is a neuromuscular phenomenon dependent on a nervous reflex and subserved by the intrinsic plexuses of the gut. The upper set of lumbar nerves carries the sympathetic impulses, and the lower set of sacral nerves carries the parasympathetic fibers.[14] A diagram illustrates this extrinsic innervation (Fig. 1). Stimulation of the sympathetic outflow inhibits peristalsis; it also tightens the internal sphincter as observed in man by Learmonth,[15] who stimulated the presacral nerve by a faradic current. One of us has repeatedly observed that grasping the hypogastric plexus with a forceps will constrict the anus around the inserted finger. Parasympathetic stimulation, on the other hand, will increase peristalsis and relax the sphincter. Acetylcholine, prostigmine, or physostigmine act through these nerves. The

third set of nerves is somatic; they are paralyzed in lesions of the cord or cauda equina.

Aside from animal experiments, in which Adamson and Aird were able to produce megacolon in cats by dividing the parasympathetic sup-

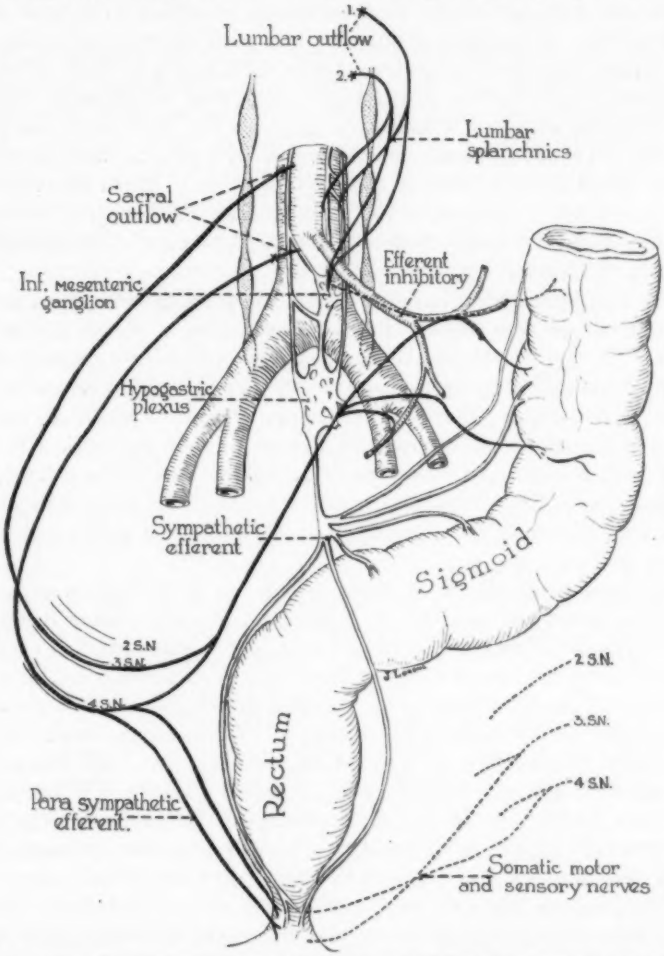

Fig. 1.—The extrinsic innervation of the colon. (Modified from drawing in L. Abel's "The Surgery of the Sympathetic Nervous System," Rodney Maingot's *Postgraduate Surgery*, Appleton-Century Co. Ltd., London, 1937.) The sympathetic outflow to the distal colon leaves the cord at the first and second lumbar segments and travels through the lumbar sympathetic, ganglionated trunk and the lumbar splanchnics to the inferior mesenteric and hypogastric plexuses. From here the fibers travel to the colon, inhibit peristalsis, and close the internal sphincter. The parasympathetic outflow leaves the cord through the lower sacral segments and travels past the left border of the interiliac triangle toward the inferior mesenteric artery. This vessel may be stripped from its origin to about 1 inch without the danger of injuring these fibers. The parasympathetic fibers contract the colon and dilate the sphincter. The somatic nerve supply to anus and the external sphincter comes from the third and fourth sacral segment. The intramural plexuses of Meissner and Auerbach are not shown in the diagram. This failure to convey a normal impulse for defecation has been one of the theories of megacolon.

ply to the colon,[16] and Burrows, by irritating the lumbar sympathetic ganglia with silica,[17] there are a number of observations on man to illustrate the effect of the two antagonistic sets of nerves. Thus, patients suffering from peripheral vascular disease, in whom lumbar sympathectomies are done frequently, show increased peristalsis as a result of a release from sympathetic inhibition. In patients with cauda equina lesions, in whom the lumbar sympathetic outflow is intact but the sacral parasympathetic outflow is destroyed, the rectal sphincter is usually patulous, the sensation of the lower rectum is lost, and the capacity for storage and thus for massive bowel movements is absent. Such a patient passes small fecal masses at frequent intervals. When all extrinsic nerves are lost, peristalsis in the gut continues satisfactorily, and even continence may be slowly restored. Obviously none of these conditions exist in megacolon.

The unquestionably favorable effects of sympathectomy in cases of megacolon have been explained by (1) diminution of plastic tone of the colon,[13] (2) allowing the weakened pelvic parasympathetic nerves to exert their action unopposed by the antagonistic sympathetic innervation, and (3) the release of a reflex sympathetic inhibition.[14] From a physiologic standpoint, this latter explanation seems the most probable. Be that as it may, it is easy to show that in man as well as in the animal, the section of the sympathetic nerve supply to the distal colon results in a release of inhibition and often in a massive defecation with a relaxation of the sphincter ani.

One final point should be made, which has a bearing on prognosis and emphasizes the urgency of combating persistent colonic distention with all available measures, and that is the unfavorable effect of maximal distention on the bowel. These effects have been summarized with the addition of many original contributions in the recent monograph of Wangensteen on intestinal obstruction.[18] The gaseous content of the bowel after obstruction of the sigmoid colon contains small amounts of O_2 and CO_2 but an overwhelming amount of nitrogen (80 per cent). We shall return to this point in our therapeutic suggestions. The other effect is the diminution of blood flow when intracolonic pressure rises. This pressure may rise from 12 to 52 cm. of water, which may exert, as Wangensteen has calculated, around 735 cm. of water pressure per centimeter surface in the cecum to 340 cm. in the descending colon. The frequency with which perforation occurs in the cecum in late or neglected cases of obstruction is immediately apparent because of the different amount of stress exerted on different segments of the bowel.

Increased intracolonic pressure influences absorption from the bowel. Absorption through the veins, through the lymphatics, and transperitoneally is greatly modified following distention. Lymphatic absorption of dyes or bacteria is greatly enhanced by obstruction. One of us has encountered large lymph channels and lymph nodes in explorations for

megacolon, and this finding may explain Finney's theory of lymphangiectasis in cases of megacolon. That these patients are toxic, dehydrated, and anemic is sufficiently known and should be remembered in outlining treatment.

DIAGNOSIS

The diagnosis of megacolon, except in early infancy, is easy and depends on the three cardinal symptoms of obstinate constipation, marked enlargement of the abdomen, and visible peristalsis. Spontaneous bowel movement is rare, and sometimes weeks may go by without evacuation. Periods of constipation may be followed by diarrhea, which may persist in spite of massive fecal impaction.

The abdomen may assume tremendous proportions especially in the upper part above the navel. The skin is thin and shiny. Tympanitic sounds are obtained, but occasionally large fecal masses may be palpated and percussed. No free fluid is present. Deep peristaltic waves are often visible, and gurgling sounds may be heard with or often without the stethoscope. The sigmoid colon is often redundant, and the loop may be visible even under the right lobe of the liver. The abdominal distention compresses the contents of the chest. The costal arches are widely separated, the diaphragm is high, the heart and lungs are pushed up, interfering with respiration and circulation. Because of the poor intake and utilization of food and liquids, the child is emaciated and dehydrated. A marked secondary anemia is often present. Sudden complications may occur in the form of ulcerations, perforation of the bowel, or volvulus of the sigmoid loop, which may cause death of the child unless promptly recognized.

In the neonatal period the diagnosis may be difficult. However, the abdomen is large and close observation will usually reveal peristaltic waves. Diarrhea may alternate with constipation, or diarrhea may predominate for the first few weeks of life, as in Case 2. Persistent vomiting during the first weeks of life is likely to occur.

This condition should not be confused with any other. However, at times congenital duodenal obstruction, early cases of celiac disease, tuberculous peritonitis, or rickets must be considered. Mechanical obstruction of the bowel should be ruled out by digital or proctoscopic exploration of the rectum. A thin barium mixture, slowly instilled under fluoroscopic control, gives an idea of the size and location of the distended loops and helps to rule out congenital strictures or bands. For a satisfactory barium enema the colon should be as thoroughly evacuated as possible. In older children a barium meal gives a better idea of the amount of stasis than the enema. The barium, however, should be diluted with equal amounts of petrolagar and may have to be evacuated with some of the parasympathetic drugs or with spinal anesthesia.

From the study of some of our cases appearing in adult life, the conclusion must be drawn that congenital megacolon may exist in a latent, symptomatic stage for many years, during which time the neuromuscular dysfunction is compensated and spontaneous bowel movements are possible. In spite of this the anatomic changes may be quite extensive (Case 9).

MEDICAL MANAGEMENT

In undertaking the medical management of congenital megacolon one has to assume that congenital strictures of the rectum are absent or, should they be demonstrable, have been dilated by daily digital dilatations which can be carried out after proper instructions to the child's mother or nurse. These strictures, as reported by Vernon David[9] and by Brennemann,[10] are situated from 1 to 2 cm. above the anus. Occasionally they must be divided surgically. It must be emphasized, however, that megacolon may persist or even progress after the removal of these obstructions, and this occurred in Case 1 of our series. Five such cases were reported by Judd and Thompson.[19]

Rectal dilatations have been systematically employed by Hurst,[6] who uses increasing sizes of conic bougies in order to induce better relaxation of the internal sphincter. That this is of great value is best demonstrated by our experience with Cases 2 and 3, both of whom have always experienced weeks of relief following manual disimpaction of the rectum. This procedure carried out under a general anesthetic naturally dilates and stretches the sphincter and may even lead to a short period of incontinence.

A number of various diametrically opposed measures have been advocated to facilitate the emptying of the colon. Some authors advocate a rough, high residue diet to promote peristalsis, others order a bland diet so that fecal accumulation may be reduced. Some urge the elimination of animal protein to decrease putrefaction, while others prescribe a buttermilk diet. Some advise abdominal massage, and others disapprove for fear of perforating a thin colon. Some push carbohydrates to restore liver glycogen, and others are afraid of increasing fermentation. Some give cathartics; others feel that they are useless, may bring an impaction, and favor ulceration in the colon.

Equal, if not more numerous, are the suggestions for drug therapy. Atropine has been given in large doses with the idea of relaxing the spasm of the sphincter; so have opium and papaverine. Saturated solutions of magnesium sulfate have been used for rectal instillations which, according to Bonar,[20] irritate the local neuromuscular mechanism. Hot tap water enemas have been found useful by Fridell.[18] Pancreatic, insulin-free tissue extract[21] and parathormone[22] have been found to empty the distended colon under roentgenologic control. The parasympathetic drugs, such as pilocarpine, eserine, prostigmine, and acetylcholine, have

been employed. The latter drug is highly advocated by Abel[23] for improving atonic constipation or postoperative ileus.

Of all these suggestions the use of high, warm colonic irrigations, the administration of mineral oil, systematic rectal dilatations, and a well-balanced diet, avoiding extremes of high or low residue, seem logical. Obviously in case of acute obstruction or as a preoperative measure, the low residue diet is preferable. When, however, with the aid of enemas and mineral oil, fairly regular evacuations have been obtained, a certain amount of roughage may be of advantage. We have seen help from small doses (1/150 gr.) of eserine administered with mineral oil, especially following sympathectomy, when such a parasympathetic drug can act without the opposition of sympathetic influence on the bowel.

In studying the possible effect of sympathetic denervation on the emptying of the bowel, spinal anesthesia has been advocated as a preoperative test.[24] It has also been noted that sometimes spinal anesthesia alone will restore functional activity for many weeks and months. Such a case has been reported by Stebins, Morton, and Scott.[25]

The indications for medical management may be briefly summarized as follows: (1) in an effort to minimize distention of the bowel and prevent nutritional changes in all infants and children up to the age of 3 years; (2) in all mild and latent cases, even after that age, if response to treatment is satisfactory and the child is growing normally; (3) as a preoperative measure, once it is recognized that the case is not medically tractable. Obviously this is the point on which most pediatricians and surgeons have disagreed in the past, all the more as the mortality of bowel resections and the frequent recurrences did not encourage pediatricians to refer their cases to surgery. With the introduction of sympathectomies in the treatment of megacolon, many of the objections against surgery will have to be revised.

We also feel that most cases of atonic constipation with long, redundant sigmoid loops, seen in adults, do not really belong to the category of congenital megacolon. Spinal anesthesia does not evacuate this colon well, and it is held by Learmonth[26] that sympathectomy is not indicated. Skillful medical management may relieve constipation. Adson,[31] however, has recently reported an excellent result in one case of adult atonic constipation by the use of splanchnic nerve section and upper lumbar sympathectomy.

SURGICAL TREATMENT

As Rankin[27] has pointed out, in deciding between medical and surgical measures, three important factors must be considered, namely, the extent of the lesion, the age of the patient, and the presence or absence of obstruction. Obviously there are many constipated children, in some of whom the x-ray may reveal anatomic anomalies such as undescended cecum, mobile cecum, and redundant sigmoid loop, who are readily

treated with simple training and medical measures. Learmonth[26] has recently studied material from the Royal Hospital for Sick Children in Aberdeen and feels that in constipated children, in whom there is an elongated and distended colon, in whom medical measures do not result in satisfactory evacuation, and in whom a barium meal reveals an intractable colonic stasis, a neurologic operation is indicated. We shall refer to the various types of sympathectomy later.

The age of the patient often contraindicates anything but emergency surgery. In our series the youngest child operated on was 5 years old, but surgical procedures have been reported at an earlier age. Obviously, in infants colonic distention must be combated with conservative measures, in spite of which they may succumb (Case 4). Whether in the future a combination of oxygen inhalations,[28] parasympathetic drugs, and continuous colonic suction will be effective in the refractory cases in infants remains to be seen. We would hardly advise surgery of any sort before 4 years of age.

TABLE II

MORTALITY STATISTICS FOLLOWING CONSERVATIVE AND SURGICAL TREATMENT EXCLUSIVE OF SYMPATHECTOMY

AUTHOR	NUMBER OF CASES	MORTALITY FOLLOWING	
		CONSERVATIVE TREATMENT PERCENTAGE	SURGICAL TREATMENT PERCENTAGE
Danziger	94	75	34
Lowenstein	2	88	22
Schmidt	119	60	40
Neugebauer	254	68	5
Schneiderlöhn	268	79	52
Judd and Thompson	42	19	23
Ask-Upmark	102	37	52

The presence of acute intestinal obstruction produced usually by volvulus of the elongated sigmoid loop may call for an immediate operation. Untwisting of the volvulus with or without ileostomy, appendicostomy, or cecostomy is imperative and may be lifesaving. Most of the acute intestinal obstructions, however, are relieved by high colonic irrigations.

Before the advent of sympathectomies for megacolon, difference in mortality following medical and surgical management was very slight. We have summarized some of the older statistics not containing sympathectomies in Table II. The last review of Ask-Upmark was based on 102 cases collected from Swedish hospitals between 1895 and 1928. Some of the patients have been followed for as long as twenty-five years. Because of these and other statistics both pediatricians and surgeons have been reluctant to advocate surgical procedures removing parts of or the entire colon. Many years ago Von Eiselsberg stated that one should either resect the colon or close up the abdomen, as sidetracking opera-

tions seemed of no avail. In a recent report on colonic resections for Hirschsprung's disease, Laqua[29] stated that the immediate mortality of one-stage resections was 25 per cent; that of several stage resections was 6 per cent.

The disconcerting phase of colonic resections, however, should not be the immediate mortality. With adequate preparation, multiple-stage operations and extensive resections are well tolerated, especially in children. However, a progressive dilatation of the segment, proximal to the resection, has been reported too often to be ignored. Even when the entire colon was removed, the dilatation extended to the ileum.[6] Our Case 1 showed this kind of secondary dilatation following resection of the sigmoid loop.

We do not wish to imply that colonic resections have no place in the treatment of megacolon for the reason that even when medical therapy or sympathectomy have been successful, the elongated, redundant sigmoid loop with its occasional kinking and twisting may produce attacks of acute intestinal obstruction. Case 2 illustrates this point because after a successful sympathectomy, which resulted in daily spontaneous bowel movements, two attacks of partial volvulus have so far occurred. Under such circumstances the resection of the redundant sigmoid loop may prevent a great deal of future trouble. In Case 1 the resection was well tolerated, but the megacolon still persists.

We now come to the indications and results of sympathectomy in congenital megacolon. The operation was first done for this condition in 1927 by Wade and Royle,[13] who did a lumbar ramisection. During the last ten years several modifications of the original operation have been described. While Learmonth and Rankin have attacked the presacral nerve and inferior mesenteric plexus,[15] Judd and Adson[30] used a lumbar sympathectomy, and lately Adson[31] suggested for severe cases the resection of the splanchnic nerves and two upper lumbar sympathetic ganglia. While both procedures interrupt the sympathetic fibers to the colon, both have effects on other organs. The Learmonth operation abolishes the contraction of the seminal vesicles and thus produces sterility in the male, although orgasm is present. The lumbar sympathectomy, if done high enough, will not affect ejaculation, but denervates both lower extremities so that they become hot and dry. In our experience this produces no discomfort or disadvantage. Finally, Telford and Stopford[32] devised the section of the medial branches of the lumbar sympathetic nerves, which avoids sterility in the male and vasoparalysis in the lower extremities. This is undoubtedly the optimal type of operation, although for a thorough denervation the lumbar sympathectomy seems preferable.

Morton and Scott[24] have made a very important contribution to the selection of the suitable cases for sympathectomy. They proposed the use of spinal anesthesia to inhibit the sympathetic outflow to the colon

and demonstrated the evacuation of the colon under the anesthetic. We have made use of this test in Case 2. However, in Case 3, a nervous, anxious child, it was impossible to get a satisfactory spinal tap, and hence, instead of inhibiting the sympathetics, we resorted to stimulating the pelvic parasympathetic outflow. This was done with an ampule of prostigmine given subcutaneously, but acetylcholine could be used equally well.[31]* In this case the response was only slight owing to the loss of contractile power of the colon, demonstrated later at operation.

In studying the musculature of the colon in Hirschsprung's disease, it becomes evident that while some cases show marked muscular hypertrophy (Cases 1, 2, and 4), some patients come to the autopsy table or are seen on the operating table (Case 3) with extreme thinning-out of the colonic wall and a complete loss of the musculature.

Whether this is a congenital defect or a result of exhaustion, muscular decompensation, and nutritional effect of constant distention, is difficult to say. But the fact remains that when the muscle power of the colon is lost, no type of sympathectomy can help, nor can rectal dilatations be of any avail. The urgency of decompressing the colon from early infancy is obvious. Our second patient, with hypertrophy of the musculature and prompt response to a spinal anesthetic, made a far more spectacular recovery after sympathectomy than the third patient, who responded poorly to prostigmine and showed a thin transparent membrane instead of a hypertrophied colon.

The results of sympathectomy for megacolon have been very promising. Provided suitable cases are selected and aftertreatment is scrupulously carried out, it offers today the best method of regulating defecation and avoiding future complications.

The preoperative evacuation of the colon is important. The patient is placed on a low residue diet with daily high enemas, mineral oil, and acetylcholine. It may take two weeks to get the colon comparatively empty. In case of fecal impaction, the rectum is dilated under general or spinal anesthesia. In a maximally distended colon, the inhalation of 95 per cent oxygen may be helpful.[28] As the children are often dehydrated, toxic, and anemic, dextrose given intravenously and blood transfusion diminish the surgical risk. While both of our sympathectomies have been done in one stage, it might be advantageous occasionally to operate in two stages by an extraperitoneal route.[31] The mortality of sympathectomies is small. Adson[31] reported two deaths following the operation. Compared with colonic resection it is a harmless procedure.

Following operation, we have placed these children on a general diet, mineral oil, and physostigmine (gr. 1/150, three times a day). They were urged to move their bowels right after breakfast. The training

*In a recent case the response to acetylcholine was used for a preoperative test.

of this habit is usually absent in these patients. Hot enemas must be kept up daily until the contractile power of the colon is regained. In Case 2 this occurred a few weeks after operation; in Case 3, only six months later. Even so, sudden impactions or incomplete volvulus may occur (Case 2).

Because the operation has only been practiced for the last ten years, it is difficult to obtain late results. Up to date over 100 sympathectomies have been performed for megacolon, but late results are not available.[34] In our own work forty-eight lumbar sympathectomies performed for other reasons resulted in one death, a mortality of 2 per cent. The best follow-up studies were presented by Ross,[33] who reviewed the end re-

Fig. 2.—Case 1. Barium enema six years following resection of the sigmoid loop. Note the huge rectal ampulla and rectosigmoid loop.

sults in seventeen cases done by the Fellows of the Association of Surgeons of Great Britain. Fifteen of these operations were completely successful, and in the other two, the condition of the patients was much improved. Generally speaking, when early results were good the benefit seemed to be lasting.

CASE HISTORIES

CASE 1.—C. S., 17-year-old girl, entered St. Luke's Hospital on April 6, 1931, complaining of belching, distention, and inability to move bowels spontaneously.

Past History.—At age of 6 years the patient was operated on for intestinal obstruction, and again at 11 years of age. Following that she had to have cathartics and enemas daily.

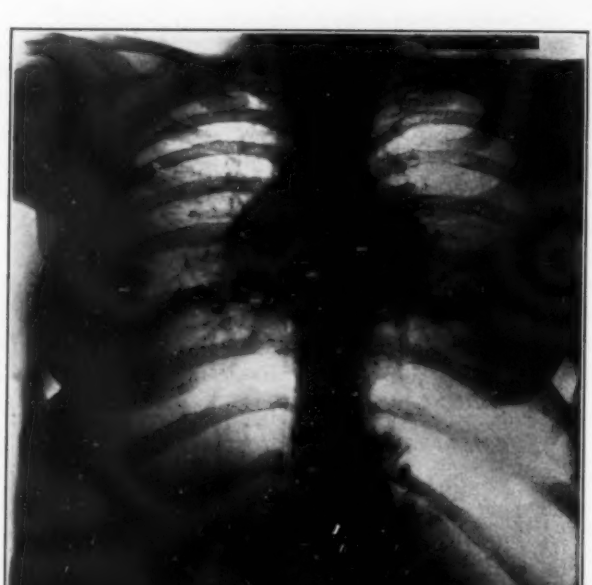

Fig. 3.—Case 1. Flat plate six years following partial colectomy. Note the high diaphragm, the compression of the chest and the pressure on the heart, increasing its transverse diameter.

Fig. 4.—Case 1. Five-hour gastric residue. This patient had frequent attacks of nausea and upper abdominal distress without a demonstrable organic obstruction.

Examination revealed an emphysematous chest, a right rectus scar, and a symmetrical, right-sided distention which would partially disappear after belching and passing flatus. There were no abnormal points of tenderness. A neurologic examination was negative. X-ray examination revealed an enormous dilatation of undetermined portions of the bowel.

Operation on April 24, 1931, by Dr. L. L. McArthur revealed an enormously dilated sigmoid loop, which was resected. The small bowel and the rest of the colon were not distended. An end-to-end anastomosis restored the continuity of the bowel. The resected bowel weighed 12 lbs. 14 oz. It had the shape of a huge U-shaped

Fig. 5.—Case 2. Barium enema before spinal anesthesia. Note the elongated sigmoid loop extending to the right hypochondrium. There is an acute angle at the sigmoid flexure, below which the sigmoid is narrow, and above which the bowel is dilated.

sausage. The individual arms were 40 and 30 cm. long. The longer arm had a diameter of 15 cm. the smaller, 9.5 to 9.8 cm.

The postoperative course was uneventful. She left the hospital on the eighteenth day. Six years later, on Aug. 19, 1937, she was readmitted, 8 months pregnant, and was greatly troubled with distention and emesis since onset of pregnancy. Enemas and knee-chest position slightly relieved the distention. A month later a normal spontaneous delivery followed. X-ray pictures taken on Oct. 9, 1937, five weeks after delivery, revealed a sigmoid and descending colon of normal caliber; at the splenic flexure the colon suddenly lost its tone and dilated to four to five times its normal size. At no point was there an obstruction (Figs. 2, 3 and 4).

Summary.—Patient with congenital megacolon was operated on twice for intestinal obstruction; sigmoid loop was resected in 1931, there was a normal delivery in 1937. Colon shows progressive dilatation above site of anastomosis. A sympathectomy is being considered.

CASE 2.—R. P., boy, was born at St. Luke's Hospital on Jan. 27, 1932, somewhat cyanotic and with a distended abdomen. He vomited since birth; atropine and a special milk formula were of little avail. The greater portions of the feeding were returned. On Feb. 14, 1932, Dr. L. L. McArthur made the diagnosis of a megacolon and felt that sympathectomy was indicated. At first, digital dilatation of the rectum was practiced several times a day, later less frequently. Three weeks after birth,

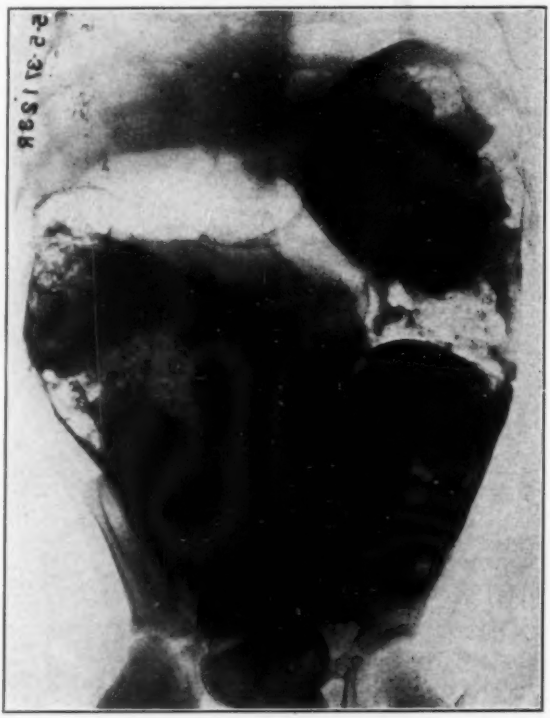

Fig. 6.—Case 2. Barium enema one-half hour after spinal anesthesia had been induced. Note the contraction of the right half of the transverse colon, the smaller diameter of the descending colon, and the proximal loop of the sigmoid. The distal loop is spastic. The child evacuated much of the barium on the fluoroscopic table.

the infant's weight dropped from 8 pounds and 3 ounces to 7 pounds and 11 ounces. At this time a fibrous ring was discovered about an inch above the anus, which constricted the tip of the fifth finger. However, rectal examination by Dr. de Bere showed a normal anus and rectum on March 15, 1932. The patient was discharged in an improved condition on March 19, 1933, and was on a Carnation milk diet. There was still diarrhea, but no vomiting. Attempts to obtain a visualization of the rectum and colon were unsuccessful.

Second admission occurred on Dec. 6, 1932, at the age of 10 months. In the interval rectal dilatations were done daily and later were reduced to once every two

weeks. Three days before admission the child refused to eat, and vomited; the abdomen had become distended and marked peristaltic waves were visible. The child was pale and emaciated. Tap water, peroxide enemas, and suppositories being of no avail, the fecal impaction was removed through a proctoscope followed by enemas. A barium enema showed a great deal of distention in the colon, especially on the right side. He was discharged and placed on a low residue diet.

Third admission was on May 14, 1934, at the age of 2 years and 4 months, for persistent constipation. A barium enema at this time revealed a colonic dilatation, especially of the transverse colon. Repeated enemas gave temporary relief.

Fourth admission, Oct. 5, 1934, revealed the same status. Bowel movement occurred only after enemas. The patient had had an acute respiratory infection.

Fifth admission was on April 3, 1935, at the age of 3 years and 1 month. He had been getting a tap water enema every second day; his bowels had never moved

Fig. 7.—Case 2. Barium enema one month after bilateral lumbar sympathectomy and resection of the inferior mesenteric and superior hypogastric plexuses. The colon has much better tonus, the diameter has markedly decreased. The elongated sigmoid loop is in evidence. Again the sharp angulation of the sigmoid loop causing a secondary mechanical obstruction is obvious.

spontaneously. Three days prior to admission he began to vomit. Oil and hot water enemas relieved the impaction.

Sixth admission occurred on April 23, 1937, at the age of 5 years. He had in the meantime been to the County Hospital for another episode, and there developed scarlet fever. He re-entered County Hospital in January, 1937, where he stayed for more than two months. At this entrance the rectum was again disimpacted, but manually. Fluoroscopic observation indicated a definite angulation of the sigmoid in the right upper quadrant, a markedly redundant sigmoid loop, and a dilatation of the large bowel extending throughout the colon. Following a spinal injection of 35 mg. of novocain, there resulted a massive evacuation of the bowel with a diminution of the size of the colon (Figs. 5 and 6). Sympathectomy was suggested,

but because of the redundant and angulated sigmoid loop, it was thought that an anastomosis between the cecum and sigmoid might become necessary.

On May 20, 1937, a bilateral lumbar sympathectomy and presacral nerve section were performed by one of us (G. de T.). The small intestine was collapsed. The entire large intestine was tremendously hypertrophic and dilated. The sigmoid loop was abnormally long with a long mesentery, and it angulated in the right upper quadrant. The abdominal wall was closed with silk. There was remarkably little postoperative reaction. A month later a barium enema showed a much smaller diameter of the colon (Fig. 7). The child still needed enemas twice a week. Three months later the patient's abdomen was flat, but he still had spells of retention. The sphincter was quite relaxed.

On Nov. 18, 1937, the patient was readmitted to the hospital because of vomiting, diarrhea, and sore throat. The abdomen was greatly distended, and visible peristalsis

Fig. 8.—Case 2. Barium enema eight months after sympathectomy. There has been a further reduction in the size of the colon. The sigmoid loop has contracted down and shows a good peristaltic wave. There is much less distention above the sigmoid flexure. This loop, however, is a potential source of acute kinking or volvulus.

was manifest. He was thought to have a partial volvulus of the sigmoid loop. The distention disappeared after a series of high enemas. A complete gastrointestinal series revealed no abnormality of motility in the upper gastrointestinal tract, but the large bowel retained some barium at the end of forty-eight hours, especially in the sigmoid. He was discharged with instructions to take a tablespoonful of mineral oil three times a day and physostigmine (gr. $\frac{1}{200}$) twice a day.

On Dec. 23, 1937, the patient still had much distention, but had had five spontaneous bowel movements in one week. Eserine was increased to $\frac{1}{150}$ gr. three times daily.

On examination on Jan. 13, 1938, eight months after operation, the patient was having two spontaneous bowel movements daily with the aid of eserine (Fig. 8). He weighed 43 pounds, a gain of 5 pounds, looked strong, and was not dehydrated.

He was last examined on March 4, 1938. Continued improvement was noted. During the previous month he had had spontaneous daily movement without the use of eserine or other medication except mineral oil. The mother had not been able to detect visible peristalsis for two months previously.

CASE 3.—W. Q., 8-year-old boy, was admitted to St. Luke's Hospital on Aug. 4, 1937, referred by Dr. E. McEnery. Since the child's birth, the mother had difficulty with his persistent distention and constipation. During the first week he began to have fecal vomiting. Repeated enemas overcame the obstruction, and he was discharged from St. Elizabeth Hospital. He failed to gain regularly. Dr. I. Abt placed the child on a buttermilk diet, which was not well tolerated. On protein powdered milk he did better. At the age of 5 years the child was at the Children's Memorial Hospital because of a convulsion. Dr. McEnery referred the patient, as distention and constipation continued to persist. Deformity of the thorax was marked.

After emptying the colon as well as possible, a thin barium-petrolagar mixture was given by rectum. The rectum and sigmoid were not dilated, in fact, looked

Fig. 9.—Case 3. Barium enema before operation. Note the short spastic sigmoid loop and the sudden dilatation at the angle between the sigmoid and descending colon. There is a huge gas bubble in the left half of the colon, elevating the diaphragm. There is a large air pocket in the ascending colon.

rather spastic. The dilatation began at the junction of the sigmoid with the descending colon and extended over to the cecum. The caliber of this dilated bowel was approximately five times the normal size. Spinal anesthesia was contemplated but was impossible because of the child's extreme anxiety and restlessness. Instead, prostigmine (1 c.c.) was given subcutaneously, which made very little difference in the caliber of the bowel (Figs. 9 and 10).

It was felt that the muscle power of the colon was seriously impaired, but a sympathectomy was still preferable and less dangerous than a total colectomy. Accordingly, on Aug. 9, 1937, through a midline laparotomy, both lumbar sympathetic chains and the presacral nerve were resected (G. de T.). The colon was enormously dilated; the dilatation started at the pelvirectal junction and ended abruptly at the

ileocecal valve. Below the pelvirectal junction the bowel seemed spastic. However, there was no mechanical obstruction at this point. The muscular coat of the colon seemed to have disappeared; the bowel was transparent and had the appearance of a fish bladder. On the left side a number of lymph glands were encountered, making a complete dissection above the second lumbar ganglion impossible.

The patient had a stormy convalescence; only repeated injections of pitressin and continuous colonic suction could relieve the distention. However, the wound healed firmly, and he was discharged two weeks after the operation and instructed for a general diet, mineral oil, eserine, and daily enemas.

There was little change in the motility of the bowel during the first two months. On Nov. 11, 1937, he had a bowel impaction, which had developed along with an anal fissure as a result of daily rectal catheterizations. The sphincter was dilated under a general anesthetic, and large quantities of inspissated feces were removed manually.

Fig. 10.—Case 3. Barium enema one-half hour after the administration of one-half an ampule of prostigmine. The air bubble in the descending colon is somewhat smaller, and there is a slight haustration visible on the medial side over the lower half of the left colon. Some of the barium in the sigmoid has been pushed into the rectal ampulla. There is, however, a very slight response to parasympathetic stimulation.

Following this, bowel movements became regular and spontaneous. On March 9, 1938, the child's abdomen was flat, and he had daily bowel movements. The rectum did not feel spastic, the fissure had healed. Enemas by catheter did not seem necessary. The child lost his toxic appearance and gained 4 pounds in three months. Barium enema seven months after operation revealed less distention and more contractility (Fig. 11).

CASE 4.—J. W., 5-week-old male infant, was admitted to St. Luke's Hospital on Sept. 22, 1935, on the service of Dr. S. C. Henn. The patient's abdomen had been distended since birth, accompanied by severe constipation; two days before admission diarrhea and vomiting set in.

Present Status.—The patient was a poorly developed male infant with a markedly distended abdomen and visible peristalsis just above and to the left of the umbilicus. He seemed in great agony. After enema and rectal tube, he had an explosive evacuation of flatus. There was no mass or stricture on rectal palpation. There was marked secondary anemia with 50 per cent hemoglobin. X-ray examination revealed no slowing of the passage of barium and a marked dilatation of the distal half of the colon (Fig. 12).

Course.—Following daily enemas, a formula of condensed milk, and rectal tube, distention and vomiting subsided for a week. On Sept. 30, 1935, he began to vomit again, and his temperature rose to 100.2° F. His diet was changed to include ten daily feedings of 2 ounces each of Eagle Brand condensed milk, diluted

Fig. 11.—Case 3. Barium enema seven months after sympathectomy. The ascending colon shows marked activity. Both ascending and descending colons have a smaller diameter. The transverse colon is still markedly dilated.

1:8. On Oct. 6, 1935, 15 c.c. of the father's blood was given intramuscularly. On Oct. 9, 1935, his red blood count was 2,080,000, white blood count 17,500, and Hb. 6.4 gm. per 100 c.c. There was anisocytosis of the red cells, normoblastic, polychromatophilic, and basophilic stippling. On Oct. 15, 1935, 60 c.c. of citrated blood was given into the left saphenous vein, and 35 c.c. was injected into the buttocks. The patient gradually went downhill, and death occurred on Nov. 23, 1935, at the age of 13 weeks (Fig. 13). Autopsy revealed a congenital dilatation and hypertrophy of the wall of the large bowel, marked anemia, marked emaciation, fatty changes in the liver, and petechial hemorrhages of the lining of the large bowel. There were no other anomalies and no mechanical obstruction of the bowel.

CASE 5.—Miss B. C., 28 years old, entered St. Luke's Hospital on the service of Dr. H. I. Meyer on Feb. 26, 1937, complaining of intermittent abdominal distention and cramping for the past year. She had always been constipated and used cathartics habitually.

Fig. 12.—Case 4, following barium enema. Note the areas of spasm between the dilated colonic segments. Fluoroscopy in such a case is far more informative. The diaphragm is high, and the organs of the chest are compressed.

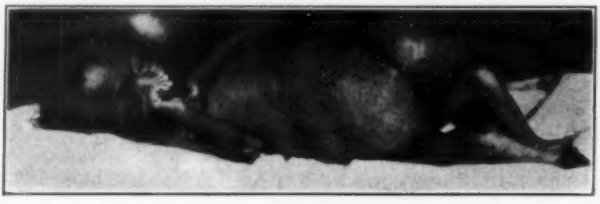

Fig. 13.—Case 4. J. W. shortly after death. Note the extreme emaciation and that the maximum of distention is above the navel.

Past History.—Following a tonsillectomy, catharrhal jaundice of 12 weeks' duration occurred. The appendix was removed in 1912.

Examination.—There was tenderness in right lower quadrant. No mass palpated and no peristaltic waves were visible.

Operation was performed on Feb. 27, 1937, by Dr. H. I. Meyer. An exploratory laparotomy revealed a dilatation and abnormal mobility of the entire colon. There was a small band of adhesions at the site of the previous appendectomy but this was causing no obstruction. The colon was dilated to about three times its normal size but was not indurated, inflamed, or obstructed. The small bowel was also distended with fluid and gas. The abdomen was closed in layers.

Postoperative Course.—Patient made a smooth convalescence and left the hospital on the fourteenth day. She remained constipated but can be regulated by enemas and cathartics.

Fig. 14.—Case 6. Cystogram reveals the bladder pushed over to the right by a fecal mass in the sigmoid. The bladder seemed to fill easily without producing a desire for micturition. Megacystis?[9]*

CASE 6.—R. B., 5 years old, entered St. Luke's Hospital on April 17, 1937, on the urologic service of Dr. Harry Culver, because of fecal incontinence and intermittent abdominal distention.

Past History.—Seven days after birth an imperforate anus was operated upon at another hospital. Following this the patient developed fair control of his bowels until November, 1936, when he had no bowel movements for ten days. After several cathartics were given, the patient developed a fecal incontinence and had five to eight bowel movements daily, which persisted ever since. At the age of 1 year the patient fell out of his buggy and was unconscious for ten days, with a resulting total blindness.

*In a tenth case, not reported, the bladder could be filled to 500 c.c., without producing a desire for micturition.

Examination revealed an alert but totally blind child with a dextrocardia, eccentric right pupil, bilateral cataracts, absence of normal anus, an artificial anus anterior to normal location, a penoscrotal fistula, and a large accumulation of fecal masses in the left lower quadrant. Cystoscopy revealed a normal urinary bladder and vesical neck. The penoscrotal fistula admitted a probe which reappeared at the anus. Cystogram showed a normal bladder pushed to the right by a mass in the sigmoid (Fig. 14). X-ray examination of the chest, abdomen, and pelvis revealed a transposition of the lung, heart, and liver to the opposite side and a typical megacolon (Fig. 15). The large bowel seemed to be in normal position.

Course.—The patient was discharged from pediatric service.

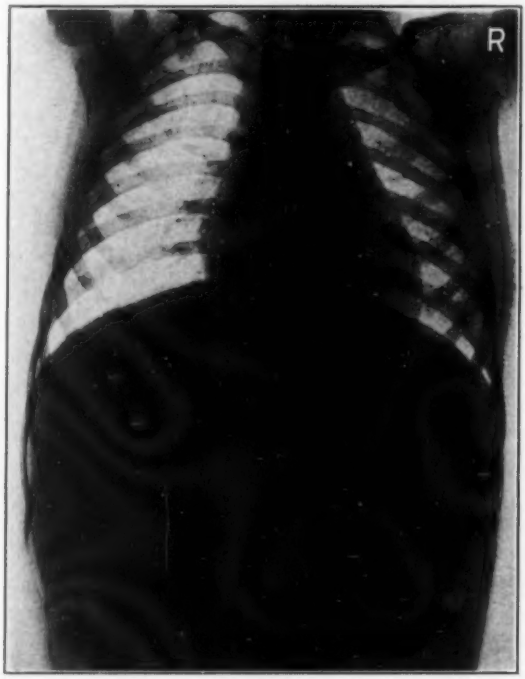

Fig. 15.—Case 6. Flat plate showing the heart on the right, the liver predominantly on the left side. The large bowel seemed to be in the right position.

CASE 7.—M. J. R., 4-year-old girl, entered St. Luke's Hospital on the service of Dr. H. E. Jones, because of distention and constipation of two weeks' duration.

Past History.—At the age of 3 years, with a high intestinal obstruction, the patient was under the care of Dr. H. E. Jones, who found a duodenal compression at the superior mesenteric vessels and performed a gastroenterostomy. She had intermittent attacks of constipation since the last admission.

Examination revealed a well-nourished child with palpable, soft masses in the right and left colon and audible peristaltic sounds. Rectal examination was negative. A barium enema showed no filling defect or obstruction in the colon. The

rectum was normal. The sigmoid was located high in the midline; the left half of the colon and the sigmoid were redundant, freely movable, and enlarged. The transverse colon was high and dilated. The cecum was located in the right upper quadrant (failure of migration).

Course.—Child was discharged after the temporary obstruction subsided. Later course is unknown.

CASE 8.—A. L., 47 years old, entered St. Luke's Hospital on July 30, 1936, on the service of Dr. H. E. Mock, complaining of severe constipation for the past ten years and spells of fainting.

Fig. 16.—Case 8, following barium enema. The distal colon is approximately five times its normal size. The sigmoid loop is very short. The barium stopped abruptly at the distal third of the tranaverse colon. Subsequent examinations revealed no mechanical obstruction at this point.

Past History.—Prior to 1917, patient had two daily bowel movements. From then on he had to use laxatives. The interval between bowel movements increased to four to five days, together with decrease in appetite and difficulty in breathing. Diet, cathartics, and large amount of water were of no avail.

Examination revealed a distended abdomen with a tight rectal sphincter. Examination by Dr. T. L. Fentress elicited a good history for genuine epilepsy. Barium enema showed that the color filled very slowly; one gallon was used to fill the distal half of the colon. The bowel was dilated five times its normal size; no barium could be forced beyond the distal half of the colon because the

patient could not retain any more barium (Fig. 16). Diagnosis of megacolon was made. Dr. C. G. Brown advised bland, bulky diet, oil retention enemas, phenobarbital, and possible sympathectomy.

CASE 9.—R. C., aged 43 years, came to St. Luke's dispensary on May 2, 1937, complaining of having lost 50 pounds in the last year and a dull pain in left chest. A physical examination revealed no significant findings. Under the care of Dr. C. G. Brown he was placed on a bland diet and sedatives. X-ray examination by barium enema revealed a huge dilatation of the distal half of the colon. The barium would not pass the splenic flexure, and at first it was thought to be caused by an organic obstruction at this level. Re-examination on June 21, 1937, showed some narrowing in the descending colon, which was thought to be the result of spasm (Fig. 17). On a bland diet and mild sedatives, the patient was symptom-free. He had never been constipated.

Fig. 17.—Case 9, following barium enema. There is a huge sigmoid loop and a marked narrowing of the descending colon, which, however, is not constant. Patient had segments of narrowing and dilatation, possibly indicative of a faulty neuromuscular mechanism.

COMMENT

It was not our purpose to give a detailed review of the present status of the knowledge on congenital megacolon; rather we wished to record certain observations which may contribute to the better understanding and more rational therapy of the disease. Obviously these patients are seen by the pediatrician in early infancy. At least 70 per cent of the cases appear within the first few weeks of life.[2] If intensive, conservative therapy is instituted, including daily irrigations, rectal dilatations and parasympathetic drugs, many children respond well. For the in-

tractable cases, after the age of 3 years, sympathectomy offers real help. However, it also has its limitations and may have to be followed by removal of parts of the colon, usually the sigmoid loop. Table III tabulates our cases.

TABLE III

CASES OF MEGACOLON

St. Luke's Hospital, Chicago, 1931 to 1937.

CASE NO.	NAME	AGE	SEX	DURATION OF SYMPTOMS	TREATMENT	RESULT
1	C.S.	17 yr.	F	Since birth	Partial colectomy	Recurrence after 2 years
2	R.P.	5 yr.	M	Since birth	Sympathectomy	Successful 18 months postoperative
3	W.Q.	8 yr.	M	Since birth	Sympathectomy	Successful 14 months postoperative
4	J.W.	5 wk.	M	Since birth	Conservative	Died at 13 weeks
5	B.C.	28 yr.	F	One year	Exploratory laparotomy	No change
6	R.B.	5 yr.	M	Since birth	Imperforate anus incised 7 days after birth	Megacolon persists
7	M.J.R.	4	F	2 years	Conservative	Intermittent fecal impactions
8	A.L.	47	M	20 years	Conservative	Not traced
9	R.C.	43	M	Sternal pain Fullness No constipation	Dietary	No change in symptoms

SUMMARY

The incidence, theories concerning its causation, and the perverted physiologic mechanisms responsible for the production of congenital megacolon have been discussed. The medical and surgical treatment, with indications and results, have been described. Nine case histories have been briefly presented. An early intensive treatment by the pediatrician in conjunction with surgical methods for the resistant cases has been emphasized.

Our thanks are due to the pediatric, surgical, and urologic staffs of St. Luke's Hospital for the permission to study the above reported cases.

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THE TREATMENT OF HYPOGONADISM IN THE ADOLESCENT MALE

BRUCE WEBSTER, M.D.
NEW YORK, N. Y.

WHEREAS the majority of cases of suspected hypogonadism in the adolescent boy are in reality only instances of delayed puberty which will eventually result in spontaneous recovery,[1] it must be recognized that a few cases have true hypogonadism which will, if untreated, persist into adulthood. The difficulties of the early separation of this group from that which will make a spontaneous recovery have led to much of the confusion in evaluating endocrine therapy in adolescent hypogonadism. The former group will recover if untreated. Yet the medical literature for the past thirty years contains innumerable reports of the cure of this condition by substances which later have been proved to be biologically inactive. A lack of knowledge of the exact mechanism of normal puberty has further complicated this differentiation. Longitudinal studies of normal adolescent boys have recently shown that the anatomic changes which constitute puberty occur in a definite sequence. Deviations from this sequence usually mean abnormality. With the development of our knowledge along these lines, it is to be expected that the recognition of the group which may persist into adulthood will be made much easier. At present these cases are rarely detected before the age of twelve or thirteen.

Although clinical endocrinologists in the past have devised many classifications of hypogonadism, most of them are without much meaning since our knowledge of the underlying pathologic processes is very slight. Clinically, these cases seem to fall into a few simple groups. The majority of cases appear to be of the so-called Fröhlich's or adiposogenital dystrophy type.[2] These cases are characterized by obesity, hypogonadism with lack of development of secondary sexual characteristics, and in many instances hypothyroidism. There exists considerable discussion in the medical literature as to whether the so-called Fröhlich's syndrome is a purely functional disturbance of the anterior lobe of the pituitary, whether a chromophobic adenoma is present, or whether there is an involvement of the adjoining hypothalamic region of the brain. From the standpoint of physiologic disturbances, it would seem that the obesity, the hypofunction of the thyroid, and the absence of gonadal development all indicate a state of hypofunction of the carbohydrate or fat metabolizing factors, the thyreotropic hormone, and the gonadotropic fractions of the anterior lobe of the pituitary. Whatever the

From the Barbara Henry Endocrine Research Laboratory of the Department of Medicine of the New York Hospital and Cornell University Medical College.

underlying etiological factor, it would appear to have produced an anterior lobe insufficiency which manifested itself by lack of development of its various functions.

The second type encountered is the so-called primary hypogonadism. These cases are characterized by overgrowth of the long bones, undernutrition, and lack of development of primary and secondary sexual characteristics. Some of these cases give a definite history of injury to, or infection of, the testes during childhood. Trauma, interference with the blood supply during operations for bilateral hernia or undescended testes, and bilateral orchitis due to mumps are the commonest causes. There are, however, other cases which appear to be due to an absence or deficiency of the secretion of the gonadotropic fraction of the anterior pituitary, with consequent testis atrophy. Why this one fraction should be deficient while the remaining ones are normal is difficult to explain.

A third type of gonadal insufficiency in the adolescent is encountered in children who have had, during adolescence, some severe constitutional disease. Severe bronchial asthma, colitis, and tuberculosis may bring about nutritional disturbances which result in lack of development of primary and secondary sexual characteristics. These cases are characterized, not by testis atrophy, but by a general arrest of genital development. Recent work would suggest that this may be due to a vitamin insufficiency.

Attempts at therapy of delayed puberty in the adolescent male have been largely along two lines. Gonadotropic substances in the form of pregnancy urine extracts and anterior pituitary extracts have been given in an attempt to stimulate the testes to secrete androgenic hormones. Thompson and his collaborators[6] reported increase in size of the genitals in adolescent boys following the administration of pregnancy urine extracts. Such therapy must be carried out over long time periods and has met with varying degrees of success. If sufficient amounts were given, and if adequate normal testis tissue was present, development of primary and secondary sexual characteristics occurred. Since many of these boys have little or no normal testis tissue, such therapy was successful in only a limited number of cases. Further, it must be remembered that many of the individuals in whom this form of therapy is successful are the ones with some functioning testis tissue which may eventually bring about spontaneous puberty.

The second form of treatment of gonadal insufficiency consisted of attempts at replacement of the androgenic or testis hormone. Koch[3] and more recently Vest and Howard[4] have reviewed the development of the androgenic hormones from the crude transplantation experiments of the early workers to the synthesis of androsterone in 1934 by Ruzicka and his co-workers.[5] Until these synthetic androgenic hormones became available, attempts at replacement therapy met with but feeble success, due largely to the difficulty of obtaining adequate amounts of the hor-

mone. McCullagh,[7, 8] Hamilton,[9] Vest and Howard,[4] Kenyon and his co-workers,[10] and others have reported genital growth and manifestations of secondary sexual characteristics following the administration of testosterone propionate to adult eunuchoids. Hamilton[9] gave testosterone propionate to five cryptorchid children. An increase in the number of erections noted was reported, but anatomic changes were not recorded. Vest and Howard[4] induced increases in size of the external genitals and the development of secondary sexual characteristics in two normal boys, aged 3½ and 9 years. Moricard and Bize[11] reported an increase in size of the penis in three children during the administration of testosterone propionate.

In the light of our rapidly increasing knowledge of the role of the androgenic hormones in the development of puberty, it seemed advisable to begin replacement therapy* in hypogonadism in the adolescent male as soon as the condition could be definitely detected. By so doing, the psychic trauma which these individuals usually undergo could be prevented, and, it was hoped, normal anatomic conditions could be brought about. Because of the known wide variation in the development of sexual maturation in the normal adolescent boy and the tendency of minor degrees of hypogonadism to undergo spontaneous recovery,[1] an attempt was made to select for this study only cases of true hypogonadism which in our opinion were likely to result in adult hypogonadism. Six cases were chosen. The majority of these individuals had been under our observation for periods varying from one to three years before the beginning of the experiment. In three cases therapy with pregnancy urine extracts had been carried out for several months without success. In each case this had been stopped for six months or longer before the present period of observation began. Of the six cases, two were typical of the so-called Fröhlich's syndrome; one was considered an instance of primary hypogonadism without history of previous disease or trauma of the testes and without evidence of other endocrine disorder; two were bilateral cryptorchids, both of whom had had previous operative procedures; and one was an example of a severe constitutional disease causing retardation of sexual development.

CASE 1.—N. Y. H. No. 154-333. J. W., of Czechoslovakian parentage, was referred to the clinic in January, 1937, at the age of 14 years because a school physician had made a diagnosis of obesity and "genital infantilism." The boy had always been healthy. He was active and moderately athletic. The father and three sisters were tall and thin. The mother was obese. Physical examination of the patient at that time showed an obese boy—weight, 69.2 kg., height, 161 cm. The breasts were prominent. The abdomen and hips were very obese. The penis was infantile, measuring 3 cm. The testes were small and soft. The prostate could not be felt. There was no axillary or pubic hair. The voice was juvenile. The basal metabolism was −18 per cent by the Aub-DuBois standard, with a pulse rate of 60. Measurements and photographs were taken and the patient was placed

*We are grateful to the Ciba Pharmaceutical Products, Inc., for the testosterone propionate (perandren) used in these studies.

on a 1000 calorie diet. There was a gradual weight loss until, in October, 1937, he weighed 64.9 kg. and was 163 cm. tall. The breasts had increased somewhat in size but there had been no other change in the physical condition. The boy was then nearly 15 years old and showed very little evidence of the increase in size of the testes which usually occurs as the first external indication of beginning puberty. Assay of the urine for androgenic hormones showed 136 color units per 24 hours. Estrogenic hormones could not be detected in his urine by our methods of assay. These hormone levels were far below the normal for boys of that age period. At this time it was felt that the boy had definite hypogonadism and would probably not undergo spontaneous recovery. He was started, therefore, on intramuscular injections of testosterone propionate in 5 mg. doses three times a week. This was continued until Dec. 16, 1937. No change in physical appearance could be detected.

On Dec. 16 the dosage was increased to 25 mg. three times a week. His weight at this time was 69.3 kg. and his height was 163 cm. By Jan. 4, 1938, a striking change in physical appearance had occurred. The weight was 73 kg. Pubic hair was beginning to grow. The penis measured 6 cm. in length. The breasts had decreased in size. Treatment was continued at the same dosage. On March 15 it was noted that the voice was deeper. Axillary hair was beginning to grow. The dosage was reduced to 25 mg. weekly. This was continued until June 20, 1938. At that time he weighed 72.5 kg. and was 169 cm. tall. The obesity of the abdomen and hips had disappeared. Pubic hair was abundant as was the axillary hair. Coarse hair had appeared on the face. The voice was deep and of adult type. The penis was 9 cm. in length. The scrotum and testes had enlarged. There was considerable increase in the degree of firmness of the testes. The prostate was palpable. In general, he exhibited a typical picture of a normal boy of 15½ years. Treatment was discontinued on June 20. One month later no evidence of regression had occurred.

CASE 2.—N. Y. H. No. 197-416. E. N. was admitted to the clinic in April, 1938, at the age of 14 years. The mother, who was of Irish extraction, was obese. The father was of normal size. The child was healthy until the age of 12 years, when he began to gain weight. At the time of admission, he weighed 52.3 kg. and was 153 cm. tall. The hips and abdomen were obese. The breasts were prominent. The penis was 3 cm. in length. The testes were small and soft. The prostate could not be detected. A few pubic hairs were present. A diagnosis of Fröhlich's syndrome was made. Because of the soft consistency and small size of the testes, it was felt that this case offered a poor prognosis for spontaneous recovery. Accordingly, beginning April 25, testosterone propionate in 25 mg. amounts was given intramuscularly three times a week. One month later, on May 24, the penis had increased markedly in size and was 6 cm. long. Pubic and axillary hair was present. The scrotum had darkened in color and was corrugated. On July 5 the penis was 8 cm. long. The testes were firm and had increased slightly in size. The voice was deep and coarse hair was present on the legs and face. The prostate was barely palpable.

CASE 3.—N. Y. H. No. 80-190. D. R., of Scotch parentage, was first admitted to the clinic in November, 1934, at the age of 10 years. The mother stated that the child was born with bilateral undescended testes and bilateral congenital hernias. At the age of 9 years, a left-sided herniotomy was performed. The hernia recurred, and he was again operated upon six months later. On admission to the clinic, a recurrent inguinal hernia was present on the left. There was a right-sided inguinal hernia. The scrotum was undeveloped. Neither testis could be felt. Pregnancy urine extracts were given daily in 100 unit doses, for six months. No change occurred.

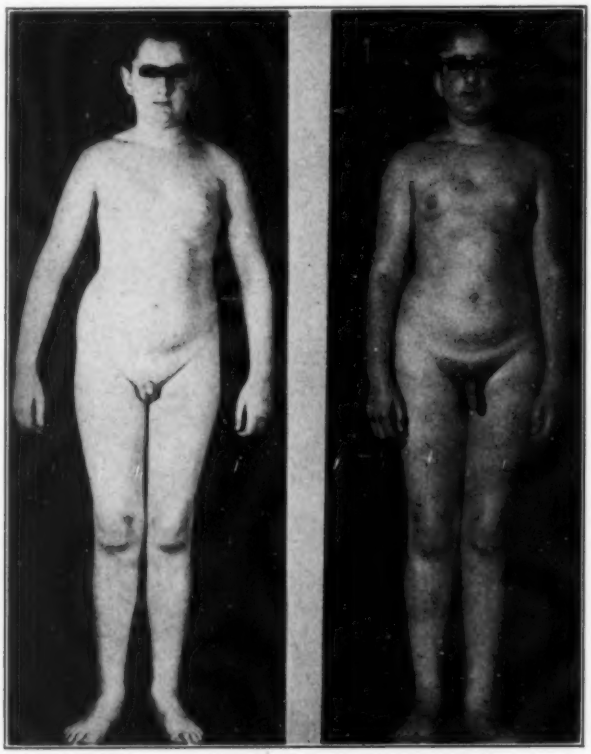
In June, 1935, an operation was performed in which the left inguinal hernia was repaired. An atrophic testis was found in the canal and was placed in the scrotum. On the right side, no evidence of testis tissue could be found. The patient was seen at intervals until January, 1938. During the entire interval

A. *B.*

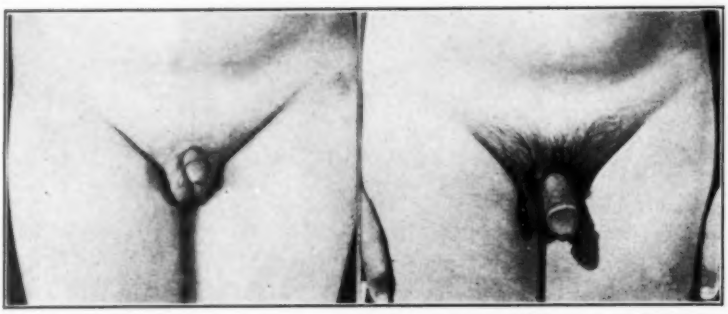
C.

Fig. 1.—Case 1. Photograph showing the appearance of the patient before beginning treatment on Oct. 20, 1937, aged 14 years and 10 months. The second photograph shows the appearance on June 20, 1938, eight months later. The third picture shows the normal genitals at the cessation of treatment on June 20, 1938.

he remained very much underweight, in spite of high calorie feeding. He was then 13 years and 6 months of age. His weight was 39.2 kg. His height was 154 cm. An atrophic left testis could be felt. The prostate could not be detected.



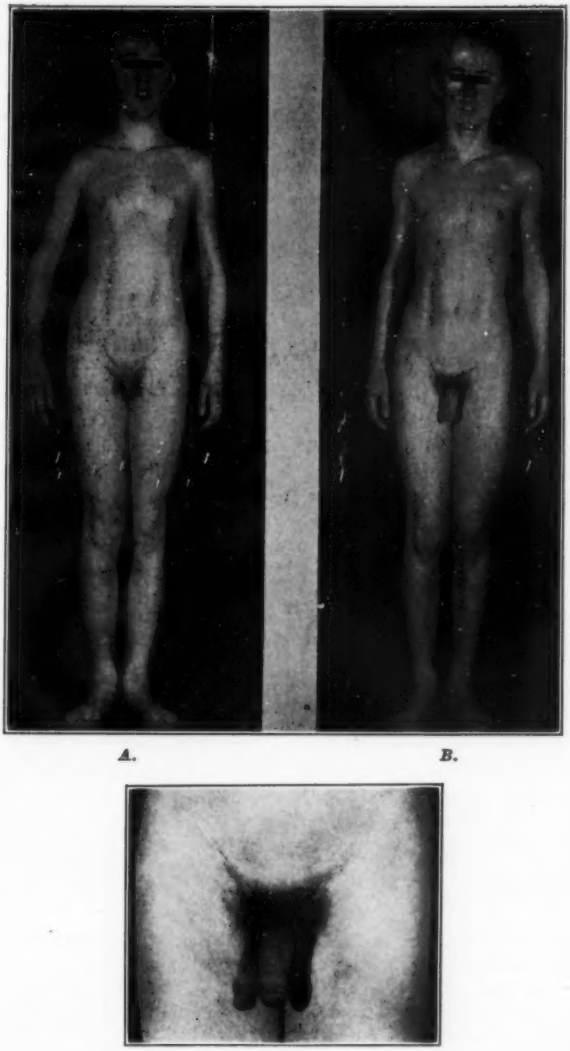
A. *B.*



C. *D.*

Fig. 2.—Case 2. Photographs showing the appearance of the whole body and genitals before beginning treatment on April 8, 1938, aged 14 years and after three months of treatment on July 5, 1938.

The penis was 4.5 cm. long. No pubic or axillary hair was present. At this time 25 mg. testosterone propionate was given intramuscularly three times a week. Four weeks later, on February 24, a striking change was noted. The body weight



A. *B.*

C.

Fig. 3.—Case 3. Photographs showing the appearance of the patient before treatment on Feb. 1, 1938, aged 13 years and 6 months, and on May 19, 1938, after three and a half months of treatment. The third photograph shows the appearance of the genitals on May 19, 1938.

was 45 kg. There had been a marked increase in the size of the penis, and the voice had deepened. Pubic hair was present. The mother remarked that the

boy exhibited much more energy than ever before in his life. On March 17 the voice was of the adult type. The penis was 8 cm. long and pubic and axillary hair was abundant. Very little change could be noted in the atrophic left testis. The dosage was reduced to 25 mg. once a week. On June 30 the weight was still 45 kg. He had grown to 162 cm. The general feeling of well-being continued. The penis was 10 cm. in length. The prostate was readily felt. There was a heavy growth of hair on the legs and face.

CASE 4.—N. Y. H. No. 42-262. F. F., of English parentage, was first seen in 1934 at the age of 9 years. He weighed 10 pounds at birth and had always been a fat child. The father and mother were both normal. There were no brothers or sisters.

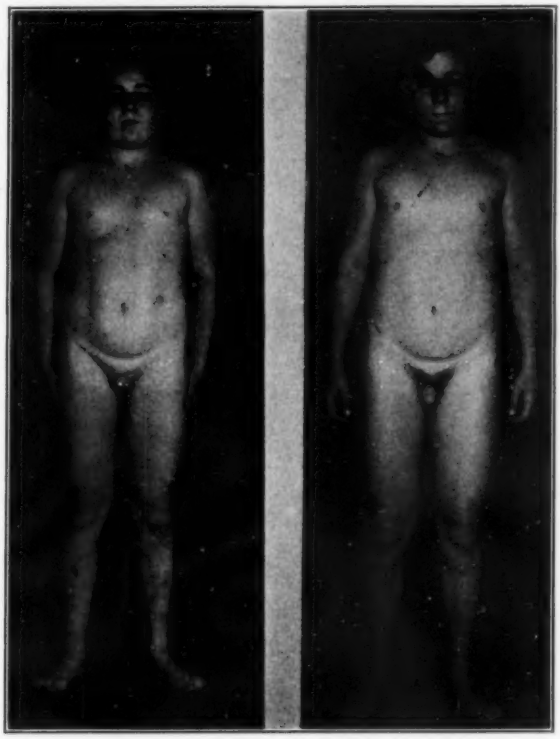
At the age of 8 years and 6 months, it was noted that the patient was a bilateral cryptorchid and that the penis was infantile. An exploratory operation was done at this time. No testis tissue could be found in either inguinal canal.

When first seen in the clinic the patient weighed 37.7 kg. and was 130 cm. tall. He was obese. There were bilateral inguinal scars. The penis was infantile. The scrotum was undeveloped. No testes could be felt. Basal metabolism was -1 per cent. Assay of the urine for androgenic hormones gave a negative result. Pregnancy urine extract was injected daily in 1 c.c. doses for an entire year beginning in June, 1935. No gonadotropic effect occurred. On Oct. 19, 1937, the patient was 13 years and 6 months old. His weight was 49.0 kg. He was 146.7 cm. tall and was still obese. The penis was infantile, being 3 5 cm. long, and the scrotum was undeveloped. At that time testosterone propionate in 5 mg. doses was given intramuscularly three times per week. By December 17, no appreciable change had occurred. The dosage was then increased to 25 mg. three times per week. Within three weeks pubic hair had appeared. On February 3, 1938, the penis was 5.5 cm. in length. Pubic and axillary hair was present. There had been considerable development of the scrotum. The prostate was palpable. The voice was deeper. On June 9 the patient was 153 cm. tall. The penis was 7.5 cm. long, and pubic hair was abundant. No testis tissue could be palpated. The voice was masculine in type, and there was hair growth on the face, arms, and legs. The dosage was reduced at that time to 10 mg. twice a week. The patient is still under observation.

CASE 5.—N. Y. H. No. 179-480. H. W. was admitted to clinic in September, 1937, at the age of 14 years and 8 months. The patient was of Austrian-Jewish parentage. The mother was obese and had a tendency to hypertrichosis. The father was tall and thin. The child appeared normal until the age of 13 years, when he began to gain weight. At that time a diagnosis of bilateral undescended testes was made, and he received injections of pregnancy urine extract for two months.

On admission to clinic he weighed 63 kg. and was 158 cm. tall. He was slightly obese. The breasts were prominent. There was some pubic hair. An infantile penis, 1.5 cm. long, was present. The scrotum was small. Two atrophic testes, approximately 1 cm. in length, could be palpated. The prostate could not be felt. A diagnosis of hypogonadism was made. There was no evidence of an intracranial tumor. Testosterone propionate in 5 mg. doses was given intramuscularly three times a week from October 21 until December 16 with no appreciable change in his condition. At that time the dosage was increased to 25 mg. three times a week. Three weeks later, on January 4, 1938, marked development of the scrotum was noted. The testes were firmer and larger. The penis had enlarged slightly. On March 3 the breasts were normal. The scrotum and testes had continued to enlarge, and the penis was 4 cm. in length. On May 1, the voice was deep and

coarse hair was present on the face, legs, and arms. On June 30, the boy weighed 71 kg. and was 166 cm. tall. There was a heavy growth of axillary and pubic hair. The penis was 6 cm. in length and the testes were approximately 3 cm. long. The prostate was palpable. The boy's features had "coarsened" and were definitely masculine. The patient is still under treatment.



A. *B.*

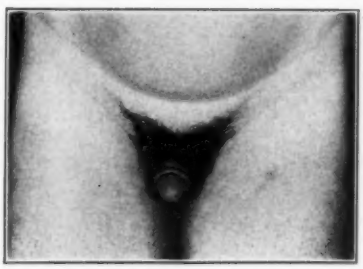


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Fig. 4.—Case 4. Photograph showing the appearance of the patient on Oct. 20, 1937, aged 13 years and 6 months. The second photograph shows his appearance on June 30, 1938, after eight months of treatment. The third picture shows the appearance of the genitals on the latter date.

CASE 6.—T. G. was referred for opinion by his physician in September, 1937, when he was 17 years of age. The boy was of English parentage. Both the father and mother were normal. The patient was a normal infant and was healthy until the age of 11 years. At that time, he developed a severe ulcerative colitis. From the age of 11 until 17 years, the patient was constantly undernourished

A. *B.*

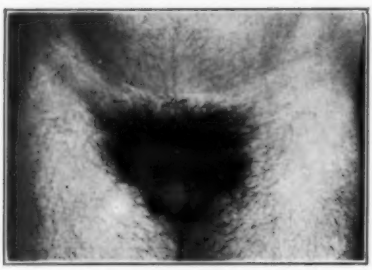

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Fig. 5.—Case 5. Photograph showing the appearance of the patient on Oct. 20, 1937, aged 14 years and 9 months. The second photograph shows his appearance on June 30, 1938, after eight months of treatment with testosterone propionate. The third photograph shows the appearance of the genitals on June 30, 1938.

and almost continually had a severe secondary anemia. His growth and physical development became arrested. When seen in September, 1937, he had the appearance of a child of 12 or 13. He was 158 cm. tall and weighed 50 kg. The face was juvenile. There was no evidence of beard growth. No axillary hair and but scanty pubic hair was present. The breasts were slightly enlarged. The penis was 4.5 cm. long. The testes were moderately firm but were approximately only 1.5-2 cm. long. The prostate was barely palpable. The pelvis was of the broad juvenile type. This case was considered an instance of delayed growth and puberty due to the nutritional disturbances resulting from a prolonged illness. Assay of the urine for androgenic hormones showed only 120 color units for twenty-four hours. During the autumn of 1937, the colitis subsided slightly but no change in growth or development occurred.

On Jan. 6, 1938, intramuscular injections of testosterone propionate, 25 mg. three times a week were started. This treatment was carried out by the referring physician. By May 16, 1938, four months later, a striking change had occurred. He had gained 8 kg. in weight and 4 cm. in height. Hair was present on the face requiring him to shave twice a week. Axillary hair was present. Pubic hair had increased in amount and was spreading over the legs and abdomen. The penis was 10 cm. long. The scrotum had developed, and the testes had increased in size. The prostate was readily palpable. The patient reported marked increase in sexual drive as well as an increase in general well-being. During this time period the colitis was only moderately active, being in much the same state as it had been in the autumn of 1937. On May 16 the dose was reduced to 10 mg. twice a week.

DISCUSSION

A consideration of the above protocols would seem to show that treatment of adolescent hypogonadism with testosterone propionate will bring about increased genital growth and the secondary sexual characteristics usually associated with normal puberty. Whether or not this form of treatment must be continued for the remainder of the individual's life, remains to be seen. Although regression of genital growth probably will not take place after the cessation of treatment, it is to be expected that small maintenance doses must be given in order to maintain libido, hair growth, and the various other functions apparently dependent upon a normal level of androgenic hormones in the blood. Although it is difficult to determine the optimum dosage of testosterone propionate necessary to bring about or maintain puberty, it was apparent from our study that 5 mg. three times a week exerted very little effect. Twenty-five milligrams three times a week seemed to be an adequate dosage. In no instance was excessive libido apparent. Smaller doses of 10 mg. two or three times a week appear to be adequate to maintain beard growth, libido, etc., after they have been established. A careful study of more cases is necessary in order to obtain additional data on the subject of clinical dosage.

Assay of the urine and blood* for androgenic and estrogenic hormones was carried out before and during treatment of these cases. These studies are as yet incomplete and will be reported elsewhere. In

*These studies were made with the collaboration of Dr. Ralph Oesting and Miss L. M. Wright.

general all six cases showed low levels of urinary androgens before treatment. After therapy there was a tendency for blood androgens and urinary estrogens to increase.

The first change which occurred in these cases following the injection of testosterone propionate was the appearance of pubic and axillary hair. An increase in size of the penis, development of the scrotum, and deepening of the voice soon followed. Growth of beard and increase in size of the prostate occurred only after several weeks' treatment. It was thought, in three cases, that an increase in size of the testes occurred. The gain in weight in Cases 3, 5, and 6 was striking and warrants further study. Although an increase in total weight occurred, these patients looked less obese at the end of the period of treatment than at the beginning. There was a decrease in size of the mammary region and abdomen. Growth spurts were noted in each case during the period of the administration of testosterone propionate. In the short time during which these patients were under treatment, no x-ray evidence of epiphyseal closure could be detected.

Because of the age of these patients, data were not elicited as to the frequency of erections and emissions. Case 6, the oldest boy of the group, reported a marked increase in the number of erections. Emissions occurred for the first time in his life. The parents of cases 3, 4, and 5 reported a marked increase in energy of these children during the period of treatment.

CONCLUSIONS

The use of testosterone propionate in six cases of adolescent hypogonadism is reported. It appears to bring about striking anatomical changes resulting in the growth of the penis, scrotum, and prostate. Secondary sexual characteristics such as hair growth and voice change occur as in the normal process of puberty. It would seem that this substance offers a means of inducing, in hypogonadal adolescent males, the anatomical changes which normally occur at puberty.

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THE HISTOPATHOLOGY OF CONVULSIVE DISORDERS IN CHILDREN

H. M. Zimmerman, M.D.
New Haven, Conn.

CONVULSIVE attacks accompany many different diseases in infancy and childhood. In such conditions as tetany, hyperinsulinism, and asphyxia, to mention but a few, the exact mechanism of the convulsions is poorly understood, but can hardly be attributed to a preexisting organic cerebral lesion. When they occur in the course of such an infectious disease as pertussis, they are frequently attributed to cerebral inflammation. In other infectious illnesses, such as pneumonia and dysentery, their mechanism is again obscure. Under such circumstances inflammatory changes in the nervous system can undoubtedly at times be demonstrated, but in a far greater number of instances no lesions are found which would produce convulsions. The changes which are seen with great regularity in the brain following such attacks are noninflammatory and are the result rather than cause of the convulsions. The presentation of evidence for this conclusion is the prime reason for the present communication.

In part, this study deals with the histopathologic findings in a group of seven children, each of whom died during or after severe convulsions or respiratory failure which occurred in the course of a serious infectious illness. An inflammatory lesion of the nervous system was considered as a possible explanation for the convulsive attacks in these patients. The post-mortem findings, however, did not substantiate this conclusion in a single instance. They did reveal a type of noninflammatory change in the brain which Spielmeyer and his co-workers have associated with epileptiform attacks, a change which they believed resulted from but did not cause the attacks.

Another part of this paper is concerned with the presentation of the anatomic findings in the nervous systems of nine other children who died as the result of either severe convulsions or asphyxia but did not have an associated infectious illness. In these cases a diagnosis of encephalitis was not ventured clinically, yet the lesions encountered during the post-mortem examinations were entirely similar to those observed in the first group. Being uncomplicated by infectious illnesses, the second group of cases more readily permitted an analysis of the pathogenetic factors underlying the cerebral lesions. When these fac-

From the Department of Pathology, Yale University School of Medicine, New Haven, Conn.

This study was aided by a grant from the Research Funds of the Yale University School of Medicine.

tors were determined with some certainty, it became apparent that they were equally applicable to the first group of cases. They will be discussed in some detail in the body of this paper.

On several occasions Spielmeyer[1-3] emphasized the role which functional vascular disturbances plays in the production of lesions in the nervous systems of epileptics. The lesions consist of necrobiotic foci in the cerebral and cerebellar cortices and especially in the cornu ammonis formations of the temporal lobes. In the cerebral cortex the ischemic necrosis of the ganglion cells has a pseudolaminary distribution and is followed by gliosis in cases of long standing. The glial scarring is

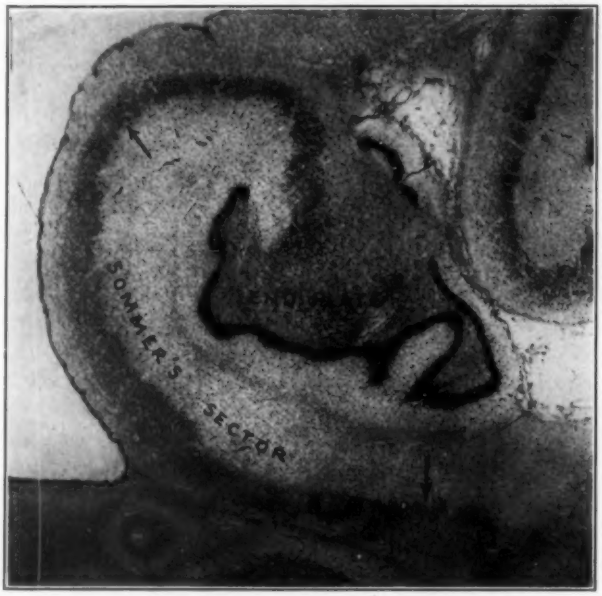

Fig. 1.—Normal cornu ammonis formation of a child 2½ months old. Between the arrows lies the vulnerable Sommer's sector. A resistant band of cells connects the latter with the end plate. Nissl stain. (×14.)

especially prominent in the subpial layer. The structures which suffer most in the cerebellum are the Purkinje cells and the small cells of the granular layer. Arborizations of microglia occur early in the molecular layer of the cerebellum, and ultimately a condition of lobular atrophy results if the cellular destruction which preceded it was extensive. The changes which occur in the cornu ammonis formations are perhaps the most important, because they are most constant and appear earliest. They also consist of ischemic necrosis of the ganglion cells, particularly of those in the vulnerable band known as Sommer's sector (Fig. 1). The vulnerability of the cornu ammonis formation was shown by Uchimura[4] to be a factor of its relatively inadequate blood supply. To

these zones of predilection Scholz[5] added the thalamus and, on the basis of his findings in idiopathic as well as symptomatic epilepsy, he concluded that the child's brain in the first year of life was especially susceptible to these lesions.

By "functional vascular disturbances" Spielmeyer meant any interference with circulation capable of producing cerebral anoxemia, exclusive of organic vascular occlusion as produced by thrombosis or embolism. He considered angiospastic phenomena to be the functional factors of prime significance, but he included also capillary and venous stasis. He was of the opinion that organically diseased blood vessels, including those that are altered by atheromatous changes, are particularly prone to vasomotor disturbances.[6] The histopathologic residua of these functional vascular disturbances are vascular stasis, capillary and "ring" hemorrhages, and the necrobiotic lesions previously mentioned.

CONVULSIONS IN THE COURSE OF INFECTIOUS ILLNESSES

Pneumonia

CASE 1.—A white male child, 4½ years of age, whose illness began with coughing and drowsiness, had generalized convulsion lasting one-half hour, followed by two similar ones and a fourth which lasted over one hour. Coma, fever, cyanosis, large, fixed right pupil, and retinal hemorrhages were present. The reflexes were sluggish. Death occurred two and one-half days after onset of illness. The case was diagnosed as bilateral diffuse pneumonia and pleurisy. Macroscopic examination showed cerebral edema and petechiae; also widespread destruction of nerve cells of cerebral cortex.

Clinical History.—The patient was born in the New Haven Hospital at full term by cesarean section. His development was normal until the onset of the last illness, which began with poor appetite and drowsiness two days before his readmission to the hospital. A slight cough appeared, but he was not particularly ill until ten o'clock the next morning when he had a generalized convulsion which lasted about one-half hour. The same afternoon two more severe generalized convulsions occurred which were treated with sodium bromide and chloral hydrate. At eleven o'clock that evening he had his fourth convulsion which lasted for more than one hour. The pupils were markedly dilated, but there was no nystagmus and no retraction of the head.

On admission to the hospital the child was comatose and cyanotic. Respirations were rapid and the temperature was 40.6° C. The right pupil was larger than the left and did not react to light. The fundi showed tremendous engorgement of the veins and several large hemorrhages. Signs of pneumonia were found in the lower lobe of the left lung. The deep reflexes were sluggish; the Babinski and Kernig signs were negative.

The child was placed in an oxygen tent, but he continued in coma and had repeated convulsions. The pneumonia spread to the right lung. In spite of intravenous glucose infusions and digitalis, he expired two and one-half days after the onset of illness.

The blood Kahn and Wassermann tests were negative. A blood count revealed 4,400,000 red blood cells and 14,200 white blood cells and a differential count of 90 per cent polymorphonuclear leucocytes. Blood culture revealed pneumococcus Type I in both the blood agar plates and the broth. The cerebrospinal fluid was

under increased pressure and contained forty-five cells per cubic millimeter, of which twenty-five were of the mononuclear variety. Pandy reaction was negative.

Necropsy.—Post-mortem examination was performed by Dr. David M. Grayzel three hours after exitus.

The bronchi and bronchioles were the seat of an acute inflammatory process. Most of the left lung, with the exception of the anterior margin, was consolidated and gray in color. The upper and lower lobes of the right lung were firm and deep red. Both pleural cavities contained a fibrinopurulent exudate. On microscopic examination the pulmonary alveoli were filled with fibrin and leucocytes.

A large amount of freshly clotted blood was present in the stomach and filled the entire intestinal tract. The only possible source of this hemorrhage was an ulcerative process in the first part of the duodenum. The ulceration was superficial, involving only the mucosa and a portion of the submucosa, and no large ruptured blood vessels were found. There was, however, a considerable amount of blood throughout the submucosa in the region of the ulceration. The latter appeared to be of recent origin since there were but few leucocytes and no fibrosis at the base.

Brain.—On macroscopic examination the only abnormalities noted in the nervous system were the presence of widespread edema and small clusters of petechial hemorrhages in the occipital lobe cortex. Histologically extensive lesions were seen throughout the cortical gray matter and even in the central gray. These consisted of destruction and disappearance of ganglion cells without any apparent changes in the glia. Entire convolutions were seen to be totally depopulated of their nerve cells (Fig. 2). Sommer's sector in the cornu ammonis formation had completely disappeared (Fig. 3). Some convolutions revealed the destructive process in zones limited to one or two laminae. The frontal, temporal, and parietal lobes were more seriously involved than the occipital. In those regions where the cellular destruction was not complete, there was, nevertheless, extensive cellular injury characterized by swelling and nuclear and cytoplasmic disintegration. This type of change was seen in nearly all the basal ganglions and was particularly striking in the hypothalamic nuclei.

CASE 2.—A white male infant, 28 months of age, whose illness began with profuse nasal discharge, fever, cough, and vomiting, had generalized convulsion lasting five minutes, followed by repeated convulsions and stupor. There was bilateral positive Babinski sign. Status epilepticus, dysphagia, papilledema and irregular respirations were followed by death on the seventh day of illness. Pneumococcus pneumonia was present. There was widespread destruction of nerve cells of the cerebral cortex.

Clinical History.—The patient, a 28-month-old white male infant, was the product of a normal pregnancy which was terminated by cesarean section because of a contracted pelvis. Subsequent development was that of a normal child.

Two days before his admission to the New Haven Hospital he developed a moderately profuse nasal discharge. Food was poorly taken that day, and by evening an elevated temperature was first noted. That night the child coughed frequently. The cough and fever persisted throughout the following day, and almost all food given was vomited. On the morning of the day of admission to the hospital he had a generalized convulsion lasting about five minutes. During the afternoon he had three or four convulsions of a similar nature.

The temperature on admission was 39.8° C. Respirations were rapid and labored. There was frequent nonproductive coughing. Stupor was so marked that it was impossible to rouse the child even with painful stimuli such as pinpricks. An occasional twitching of the right side of the face was noted. The right arm and leg were spastic, the left, flaccid. The tendon reflexes were in general sluggish, less active on the left than on the right. There was a bilateral extensor Babinski phenomenon. Abdominal reflexes were absent. There was moderate dullness to per-

cussion over the entire right side of the chest, and over this area the breath sounds were diminished. Roentgenographic evidence of consolidation in the lung was demonstrated for the first time on the third day after admission.

The subsequent course in the hospital was exceedingly stormy. The child had frequent convulsions which were difficult to control with the usual sedative drugs. During the nonconvulsive periods there was a persistent twitching of the facial muscles and a definite tendency for the eyes to deviate to the right. During the

Fig. 2.

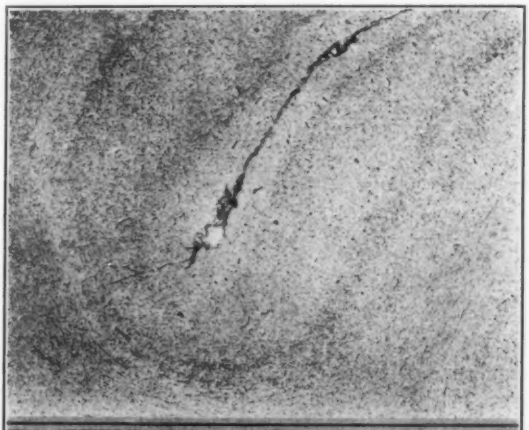

Fig. 3.

Fig. 2.—Case 1. Photomicrograph of the cerebral cortex at the depth of a sulcus. The usual lamination is obliterated because of the disappearance of nearly all the ganglion cells. The glia alone remains uninjured. Nissl stain. (×16.)

Fig. 3.—Case 1. The entire Sommer's sector is devoid of ganglion cells, but the resistant band persists. Nissl stain. (×11.)

succeeding days the spastic condition of both right extremities became more marked. Dysphagia developed on the fifth day. Papilledema gradually appeared. The day before the death of the child, which occurred seven days after the onset of the illness, respirations became very shallow and irregular.

The important laboratory data were as follows: Red blood count 5,800,000; hemoglobin 100 per cent (Sahli); white blood count 22,000; leucocytes 75 per cent;

lymphocytes 25 per cent. The spinal fluid was normal except for moderately increased pressure. The blood cultures were repeatedly positive for pneumococcus Type IV. The Kahn test on the blood was negative.

Necropsy.—A complete examination was performed seventeen hours post mortem. The tracheal mucosa was congested; the peritracheal lymph nodes were large and succulent. Both lungs contained extensive zones of consolidation in which fibrin and leucocytes were present in abundance microscopically. The pleural cavities contained a fibrinopurulent exudate.

Brain.—The cerebral parenchyma was of the usual consistency and revealed neither congestion nor hemorrhages. Microscopically, the cortical cytoarchitecture was destroyed by degenerative lesions which varied in extent from place to place but were everywhere essentially of the same type (Fig. 4). They consisted of necrosis of the ganglion cells, involving sometimes one and sometimes another of the cortical laminae. Frequently all the ganglion cells of several contiguous convolutions were wiped out. The cells which had not disappeared completely were swollen and showed chromatolytic changes. In hematoxylin-eosin preparations these cells showed

Fig. 4.—Case 2. The ganglion cells in all six cortical layers are destroyed. There is some proliferation of the subpial protoplasmic glia. Nissl stain. (×25.)

marked eosinophilia as well as pericellular edema. The capillaries in the cortex had a thickened, hyaline appearance. Associated with the ganglion cell damage was a proliferative response on the part of the glia. The protoplasmic astrocytes were particularly numerous beneath the pia and the microglia, in the deeper layers. Destroyed myelin fibers were found in the cerebral cortex and subcortex.

Comment.—Convulsive episodes are not infrequently encountered in the course of pneumonia in children. When they assume the nature of status epilepticus, and especially when coma and changes in the reflexes supervene, the suspicion of an inflammatory encephalitic process is aroused. This diagnosis was not confirmed in either of these two cases, for the cerebral lesions found at necropsy were not of an exudative nature. They corresponded in every important detail rather to the lesions which have been described in cases of epilepsy where they have been attributed, as already briefly outlined, to vascular disturbances

of a functional nature. In the first case, that of the child who survived the onset of convulsions for two and one-half days, the presence of cerebral edema and petechiae tended to support this view. In the second case, which has been reported previously in more detail,[7] there was already considerable evidence of glial proliferation in addition to the widespread cortical necrobiosis. This could easily be accounted for by the fact that the child did not die until seven days after the onset of convulsions.

Pertussis

CASE 3.—A poorly developed white female child, aged 18 months, had pertussis which lasted five weeks and culminated in generalized convulsions and loss of certain reflexes, resulting in death after eighteen hours. Microscopic examination revealed organizing bronchiolitis and pulmonary emphysema. There was destruction of nerve cells in the cerebral cortex, vascular congestion, and "ring" hemorrhages.

FIG. 5.—Case 3. The third layer of the temporal lobe cortex has a bleached appearance due to the loss of ganglion cells. Nissl stain. (×25.)

Clinical History.—The patient was an 18-month-old white female who presented a feeding problem almost from birth. She was breast-fed only for the first three weeks of life and was then given a formula. She remained rather weak and poorly nourished and was backward in her development. The first tooth appeared at thirteen months; she did not sit up until 14 months of age and never learned to creep or walk.

The present illness began with an attack of whooping cough from which three other children in the family were suffering. The illness was moderately severe but progressed without untoward symptoms for five weeks. At three o'clock one morning, however, she had a generalized convulsion and shortly after that began to convulse almost constantly. In this condition of status epilepticus she was brought to the New Haven Hospital where her temperature was found to be 40.8° C. She was semicomatose. The pupils were large and fixed; there were no hemorrhages in the fundi. Bronchial breathing and coarse râles were heard in the chest. All the extremities were flaccid and the reflexes were sluggish.

Clyses and infusions of saline and glucose were given soon after admission. A slight internal strabismus developed. Ocular movements were conjugate, and there was no nystagmus. Corneal reflexes were absent. A response to noise could not be elicited, but responses were made to painful stimuli. The deep reflexes in the arms as well as in the abdominal region disappeared. Generalized convulsions continued in spite of avertin, and the patient suddenly expired after a particularly severe convulsive attack. This occurred eighteen hours after the initial convulsion.

Laboratory examinations revealed a negative blood Kahn test and a negative blood culture. Red blood cells numbered 4,100,000; white blood cells were 43,000 per cubic millimeter; the differential count showed 49 per cent leucocytes and 43 per cent lymphocytes.

Necropsy.—The necropsy was performed by Dr. David M. Grayzel one and one-half hours post mortem.

The anterior margins of both lungs contained subpleural emphysematous bullae. There were no zones of frank consolidation in either lung. Microscopic examination revealed ruptures of many alveolar walls permitting interalveolar communication. A few bronchioles were seen to contain an exudate of leucocytes in their lumina, and in some bronchioles the exudate was being organized.

Brain.—Both cerebral hemispheres were well developed. The meninges were thin and translucent. Macroscopic examination of the brain revealed no abnormalities, and histologically the meninges and cerebral parenchyma contained no exudate of any sort. The vessels in the occipital cortex were engorged with blood, and there were even a few "ring" hemorrhages present in this part of the brain. In the insular cortex the vessels were surrounded by greatly dilated Virchow-Robin spaces. Large zones of injured ganglion cells were seen in the vulnerable bands of both cornu ammonis formations. The third and fifth layers of the hippocampal cortex lacked many of the ganglion cells, producing a bleached or faded appearance in Nissl preparations (Fig. 5). Some of the remaining nerve cells in these parts of the brain were shrunken and hyperchromatic, and a few showed pericellular incrustations.

CASE 4.—A white female infant, 11 months old, contracted pertussis along with three other siblings. There were rapid and difficult respirations, fever, cyanosis, and disorientation. The head was retracted, the back arched, and the extremities spastic. There was coma, breathing was gasping and irregular. The eyes deviated to the left. Death occurred twenty-four hours after onset of respiratory difficulty. The case was diagnosed as pulmonary emphysema and focal pneumonia. There was destruction of ganglion cells of the cerebral cortex.

Clinical History.—The child contracted a cold and pertussis two weeks before admission to the New Haven Hospital. Two older sisters and a brother had whooping cough at the same time. One week after the onset of illness the patient began to whoop and vomited about once a day with her paroxysms of coughing. She developed a high fever associated with labored and rapid respiration. On the day of admission to the hospital the mother found the infant motionless and staring off into space. The physician who sent the child in to the hospital diagnosed the condition as pneumonia and meningitis.

The temperature was 39.5° C., and the pulse rate 180 per minute. The child appeared seriously ill, disoriented, and out of touch with the environment. Breathing was laborious, and cyanosis was present. The head was retracted, and the back arched; the extremities were slightly spastic. A few scattered petechiae were present on the sclerae and trunk. The anterior fontanel was large and sunken. Both eardrums were red and bulging. For the most part, the lungs were hyperresonant, but dullness was found over the right base.

Gram-positive diplococci were present in the purulent exudate obtained by myringotomy. Dyspnea and cyanosis persisted, requiring adrenalin and carbon-

dioxide therapy. The child lapsed into coma and failed to respond even to painful stimuli. Breathing became gasping and irregular, and the eyes deviated to the left. At no time during the course of the illness were any actual convulsions noted, but the body was held in tonic contraction for several hours before exitus, which occurred twenty-four hours after admission to the hospital.

The spinal fluid was clear and contained no leucocytes and only one lymphocyte per cubic millimeter. Blood culture revealed pneumococcus Type IV.

Fig. 6.

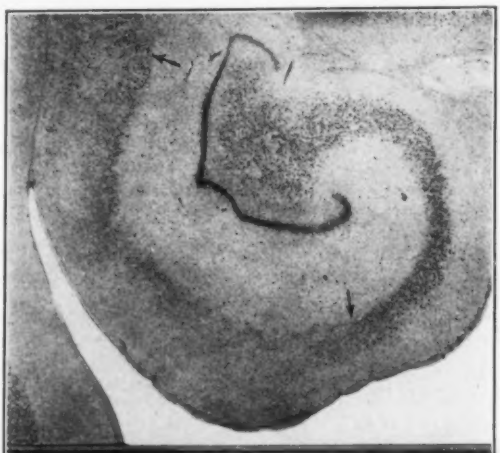

Fig. 7.

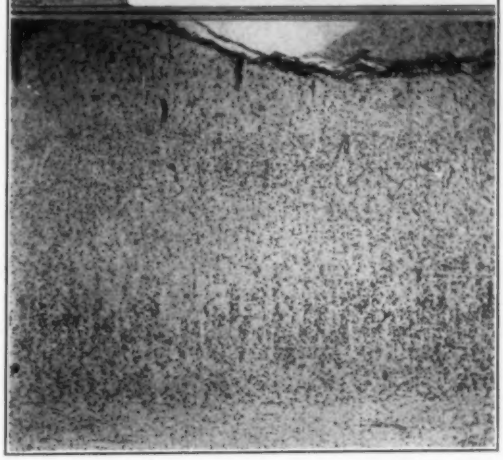

Fig. 6.—Case 4. Many of the ganglion cells in Sommer's sector (between arrows) of the cornu ammonis formation have disappeared, but those in the resistant band are well preserved. Nissl stain. (×13.)

Fig. 7.—Case 4. The cytoarchitecture of the cerebral cortex is altered by an almost complete loss of ganglion cells in the third layer. There is a moderate increase in the glia of the subpial layer. Nissl stain. (×40.)

Necropsy.—Post-mortem examination was performed by Dr. Lincoln Opper twelve hours after exitus.

Both lungs were extremely emphysematous except for the lower lobe of the right lung which was consolidated, deep red in color, and friable. Small fresh hemorrhages

were scattered through the parenchyma of both lungs. The bronchi and bronchioles were filled with tenacious purulent exudate and their mucosa was deeply congested. Microscopic examination of the pneumonic lobe of the right lung revealed leucocytes and fibrin in the alveoli.

Brain.—There were no lesions found on macroscopic examination of the brain. The leptomeninges over the left postcentral gyrus were discolored with a small amount of blood, but there was no evidence of exudate anywhere in the subarachnoid space.

On histologic examination some ganglion cells in almost every cerebral gyrus were altered by an ischemic type of change. This cellular injury reached its maximum in the cornu ammonis formations, the calcarine regions of the occipital lobes, and the postcentral gyri. In the cornu ammonis formations the ischemic change progressed to a point where many nerve cells disappeared completely (Fig. 6). Even the end plate had many ischemic ganglion cells. In other cerebral gyri it was usually the cells of the third cortical layer which were most severely injured (Fig. 7). An occasional Purkinje cell in the cerebellar cortex was similarly affected, but the granular cells were well preserved.

Comment.—Changes such as these two cases presented were described by both Husler and Spatz[8] and Neubürger[9] in the nervous systems of children who succumbed to pertussis with convulsions. Whereas Husler and Spatz considered the etiology of these changes to be some form of toxin and the whole process a toxic encephalitis, Neubürger felt that the lesions could be explained on the basis of air emboli. He believed that the increased pulmonary pressure in whooping cough led to rupture of the delicate lung capillaries through which large amounts of air were introduced in the cerebral circulation. Spielmeyer,[1] however, felt that the lesions were best explained on the basis of functional vascular changes.

In our third case the presence of vascular congestion and "ring" hemorrhages supports this view of Spielmeyer. It is not difficult to see how the severe convulsions would affect the intrathoracic pressure in a manner conducive to venous and capillary stasis and hence cerebral ischemia. All the circumstances in this case were similar to those in the first two. But the fourth case is not as readily explained inasmuch as the child did not convulse. Nevertheless, respiratory difficulty and cyanosis were prominent features in this child's clinical history and apparently were as effective in inducing cerebral ischemia as are convulsions. That this is actually so will be demonstrated in some of the subsequent cases.

Peritonsillar Abscess

CASE 5.—A white male infant, 6½ years old, suddenly developed status epilepticus which ended fatally in about six and one-half hours. He lost consciousness and became cyanotic. There was fever. Necropsy revealed peritonsillar abscess, capillary stasis and hemorrhages in the brain, ischemic cell changes, and destruction of ganglion cells in the cerebral cortex.

Clinical History.—On arising from bed about ten hours prior to admission to the hospital, this 6½-year-old child said that he did not feel well and wanted no breakfast. Shortly afterwards he complained of being chilly and toward evening, rather suddenly, had a generalized convulsion which lasted one and one-half hours.

He was sent to the Meriden Hospital, Meriden, Conn., where the ordinary sedatives and a spinal puncture were of no avail in stopping the convulsions.

The child was fairly well nourished and well developed. He was unconscious and cyanotic; breathing was stertorous. The temperature on admission was 107.6° F.; the pulse rate was 156 per minute and irregular. The heart was pounding, but there were no murmurs and no enlargement. The throat could not be examined because the jaws were tightly closed.

The spinal fluid was under normal pressure and fell rapidly when 10 c.c. were withdrawn. It was clear and contained only two lymphocytes and one leucocyte per cubic millimeter. At the end of about five hours of constant convulsions, the child died.

Necropsy.—The examination was made by Dr. J. A. Ferguson about twelve hours after death.

The only lesions encountered outside the nervous system were in the posterior pharynx, which was swollen and intensely congested. Both tonsils were deep red,

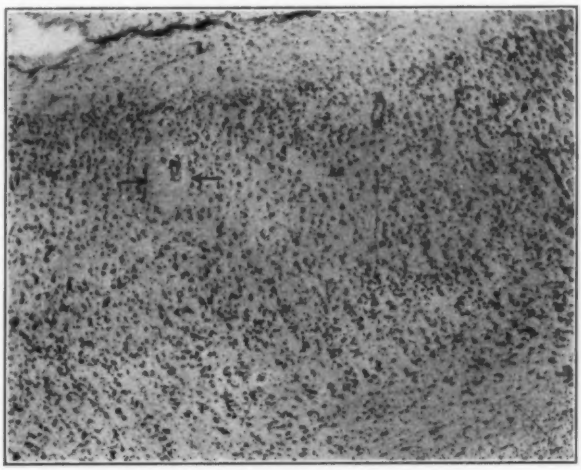

Fig. 8.—Case 5. The arrows point to a "ring" hemorrhage in the cerebral cortex. The cellular architecture is somewhat altered by the disappearance of ganglion cells. Nissl stain. (×65.)

and the left one contained a small quantity of pus which was easily expressed from it and the peritonsillar tissues.

Brain.—The cerebrum was covered by intensely congested leptomeninges. There was no cerebral swelling or edema. The subcortical vessels were engorged and many petechial hemorrhages were found in the white matter of the brain. Abnormalities were not discovered macroscopically in either the basal ganglions, cornu ammonis formations, or occipital cortex.

Many pial and parenchymal arterioles and capillaries were found congested on histologic examination. Small hemorrhages were found widely distributed in the cerebral cortex and subcortex as well as in the medulla (Fig. 8). Some of these were of the "ring" type. The ganglion cells of the cortex in general had a shrunken appearance, but only in the temporal and occipital lobes had they disappeared in sufficiently large numbers to alter the cytoarchitectural appearance. Ischemic cell change was present in the cornu ammonis formations and occipital lobes. Capillary stasis only was present in the cerebellum.

Comment.—In this instance the necrobiotic changes in the cerebral cortex were less conspicuous, and the capillary congestion and hemorrhages were more striking than in the previous cases. The survival of the child for only six and one-half hours after the onset of the convulsive attacks undoubtedly influenced the limitation of the necrobiotic lesions.

Bacillary Dysentery

CASE 6.—The patient was a white male child whose illness began with a chill lasting five minutes. Three hours later stupor, delirium, fever, and rapid pulse rate developed, along with bacillary dysentery, with mucus and blood in the stools. Generalized tonic convulsion, lasting twenty minutes, was followed by a similar convulsion two hours later. There was a succession of tonic and clonic convulsions, each lasting about two minutes and more marked on right side. Respirations were labored and rapid; there was cyanosis. Death occurred four hours after the initial convulsion. Cerebral edema and destruction of nerve cells in cerebral cortex, especially cornu ammonis formations, were noted.

Clinical History.—Two weeks before admission to the New Haven Hospital the patient had a cold, rhinitis, and an elevation of temperature. He was in bed for four days and then apparently recovered. At 8:30 P.M. of the day of admission to the hospital the child had a chill which lasted five minutes, following which he slept restlessly. At 9:00 P.M. he vomited and appeared flushed. At 11:00 P.M. the father noted that the child failed to recognize him. He became stuporous, irrational, and delirious, and was brought to the hospital in this condition.

It was learned that the patient's brother was hospitalized three days previously with bacillary dysentery. The parents had both had diarrhea, and the father was still suffering from this ailment. In the summer of the preceding year the patient and his oldest sister, aged 11 years, had diarrhea for three or four days. A cousin, 1½ years old, visited the family that summer and developed a diarrhea the following day. The family's drinking water is obtained from a well.

On admission the patient's temperature was 40.4° C., the pulse rate 180, and the respirations 36 per minute. He appeared acutely ill and was stuporous but could be aroused. Reflexes were normal.

He remained semicomatose until noon of the following day, when he appeared brighter and took fluid by mouth. Frequent loose stools containing mucus, pus, and streaks of blood were passed. He did well until 4:00 P.M. of that day, when he vomited and again lapsed into coma. At 7:00 P.M. he had a generalized tonic convulsion lasting twenty minutes, which was relieved with intravenous magnesium sulfate. Two hours later a similar seizure occurred, followed by a period of quiet until 11:30 P.M., when he began to have tonic and clonic convulsions in succession, each lasting about two minutes. These seizures continued with more marked involvement of the right side of the body. Respirations became more rapid and labored, and cyanosis appeared. Following a vomiting spell at 1:00 A.M., respirations ceased, death occurring four hours after the initial convulsion and approximately thirty hours after the onset of the present illness.

Urinalysis revealed three-plus sugar but no acetone and no cells in the sediment. A blood count showed 5,170,000 red blood cells and 39,800 white blood cells. The differential count was 89 per cent leucocytes and 9 per cent lymphocytes. Blood Kahn test was negative. Stool culture yielded dysentery bacilli, but blood culture was negative. The spinal fluid was not examined.

Necropsy.—Post-mortem examination was performed by Dr. Robert Tennant, Jr., eight hours after exitus.

There was a generalized lymphoid hyperplasia, with especial involvement of Peyer's patches and solitary lymph follicles of the intestines. The mesenteric lymph nodes were enlarged, measuring 1 to 1½ cm. in diameter. In the collapsed intestinal tract there was found a small quantity of milky white, tenacious mucoid material. The mucosa of the intestines was injected, and on microscopic examination was seen to contain numerous small "punched out" ulcers which were localized to the regions of the Peyer's patches and lymph follicles. The whole wall was edematous and infiltrated with mononuclear cells and eosinophilic leucocytes.

Brain.—The brain was edematous and its convolutions were flattened. A well-marked cerebellar pressure cone was present. The cerebral meninges were free of exudate and hemorrhage. The vessels in the centrum ovale were quite congested. In several gyri the normal cortical cytoarchitecture was blurred. This was caused by the fact that many of the ganglion cells were shrunken and stained poorly, whereas others had completely disappeared. Some appeared waterlogged and showed extensive chromatolytic changes. In the cornu ammonis formations many of the ganglion cells of Sommer's sector were absent (Fig. 9).

Fig. 9.—Case 6. The bleaching of Sommer's sector (between arrows) is due to destruction of its cellular components. Some of the injured cells, however, still persist (death of child only four hours after initial convulsion). Nissl stain. (×11.)

Comment.—As in Case 5, the full extent of the cortical cellular destruction was not reached because the survival of the child was a matter of only four hours from the initial convulsive attack. The cerebral edema and subcortical vascular congestion, as well as the necrobiotic changes which were present, were referable to the convulsive attacks and their concomitant intracranial vascular disturbances.

Upper Respiratory Tract Infection

CASE 7.—A 5-year-old white girl became anorexic, feverish, and drowsy; she vomited once, had generalized convulsions, and lost consciousness. The pupils were unequal. Repeated generalized convulsions were followed by status epilepticus. Death came on the thirteenth day of illness, with fever of 107° F. There was destruction of nerve cells of the cerebral cortex.

Clinical History.—This 5-year-old white girl was well until about five days before admission to the Children's Hospital, Boston, when she became anorexic and feverish and vomited once. She then recovered and felt better until the day before admission, when she became drowsy and slept a considerable part of the time. Two hours before admission she had a generalized convulsion and lost consciousness.

The child was well developed and well nourished. The eyes were pulled over to the left and occasionally rolled back. There was no acetone on her breath. Her color was good and respirations were normal. Nevertheless, she was semicomatose and did not respond to stimuli. The left pupil was slightly larger than the right; both fundi showed slight haziness of the disks. A moderate amount of postnasal discharge was noted, and the pharynx was slightly injected. She had had no exposure to contagious diseases.

Soon after her admission to the hospital she began having generalized convulsions which could be controlled only with sodium luminal, avertin, or paraldehyde. When not under the influence of these sedatives, the child convulsed almost constantly. She

Fig. 10.—Case 7. Extensive destruction of ganglion cells is present in Sommer's sector. The end plate is similarly involved, but to a lesser degree. Nissl stain. (×11.)

never regained consciousness after the onset of the illness and died on the thirteenth day. Her temperature rose on that day to 107° F., but it had been between 101° and 102° F. throughout most of the illness.

Laboratory examinations revealed four-plus acetone in the urine. Red blood cells numbered 4,360,000 per cubic millimeter; white blood cells were 5,800 per cubic millimeter, with a normal differential count except for a high lymphocytic-monocytic ratio. The spinal fluid on repeated examination, which included culture, was entirely normal. The blood Wassermann reaction and the tuberculin test were negative. Repeated blood cultures were negative; blood calcium was 9.7 mg. per cent; blood sugar was 129 mg. per cent.

Necropsy.—Post-mortem examination was limited to the intracranial contents and was performed at the Children's Hospital, Boston, under the direction of Dr. Sidney Farber. Fresh tissue from the cerebellum and occipital lobes was injected into monkeys, with negative results.

There was no macroscopic evidence of meningitis or a parenchymal inflammatory lesion. On microscopic examination, also, the meninges were found to be free

from exudate. The cortex of all the cerebral lobes, except the temporal, presented a normal cytoarchitectural appearance. In the cornu ammonis formations there was extensive necrosis of the ganglion cells in Sommer's sector (Fig. 10). The blood vessels in this part of the brain were not altered, and there was no proliferation of the glia. Many of the Purkinje cells in the cerebellum had disappeared, leaving behind focal glial proliferations in the molecular layer. The putamina also showed destruction of their ganglion cells, and here the lesion was associated with vascular thickening and hyalinization and with the proliferation of microglia.

Comment.—A limited post-mortem examination precluded the determination of the exact nature of the underlying infectious disease. The symptoms pointed so overwhelmingly to the nervous system that they overshadowed the clinical picture. There is thus left the meager evidence of a postnasal discharge and an injected pharynx to indicate an upper respiratory tract infection as the illness which initiated the repeated generalized convulsive attacks. The changes in the nervous system, contrary to indicating an inflammatory condition, which could cause these attacks, were of a type which has been shown in all six previous cases to have resulted from cerebral ischemia and, except in one instance (Case 4), from the convulsions themselves.

CONVULSIONS WITH MALNUTRITION

CASE 8.—A black male child, 3 months old, had marasmus from improper nutrition. Stimulants were required after the sudden cessation of respiration. There was a generalized convulsion, and respiratory difficulty for twenty-two hours resulted in death. There was widespread destruction of nerve cells of the cerebral cortex.

Clinical History.—The patient was a black male infant, 3 months of age, who was born in the ambulance on the way to the hospital after a normal pregnancy and with a breech presentation. The birth weight was 3,700 gm.

The mother, aged 18 years, was a known syphilitic who had received treatment in the New Haven Hospital. Her serology was negative at the time this child was born. She had one other child, a boy 2 years old, who was well; she had no other children or pregnancies.

The patient was breast-fed for the first 3 weeks of life and was then placed by the mother on a formula of 1 tablespoon of condensed milk in 32 ounces of water. Of this, he received 8 ounces every four hours for a period of five weeks. He then began to vomit and took but four ounces of the formula at a feeding. One teaspoonful of cod-liver oil and one-half glass of orange juice were given twice daily. He is said to have done well on this regime except that he gained no weight. At the age of 8 weeks, when he began refusing half his formula and to vomit, the loss of weight became continuous.

On admission to the hospital the infant was poorly developed, poorly nourished, and extremely dehydrated. The temperature was 95.4° F., and his weight was 3,000 gm. The skin was loose and flabby, and the eyelids were puffy.

Immediately after admission he was started on parenteral fluids, saline and glucose, and was given a transfusion of 75 c.c. of blood. On the morning after admission the infant suddenly stopped breathing for several moments and then breathed shallowly and slowly. Caffeine sodiobenzoate, adrenalin, carbon dioxide, and artificial respiration were employed, with little success. Four hours later he had a short period of tonic contractions of the entire body, the hands being held in carpal spasm. Five c.c. of calcium gluconate were given intramuscularly. The following

morning, some twenty hours after the onset of respiratory difficulty, he once more developed weak, shallow respirations which became Cheyne-Stokes in type; he died two hours later.

The blood Kahn and Wassermann reactions were both negative. The red blood cells numbered 4,290,000 and the hemoglobin 76 per cent on admission. There was no albumin, sugar, acetone, or diacetic acid in the urine.

Necropsy.—Post-mortem examination was performed by Dr. David Gaiser within three hours after exitus.

The body weighed 2,910 gm. and measured 55½ cm. in length. Practically no subcutaneous adipose tissue was present. Examination of the accessible bones, including the skull, ribs, and left femur, revealed no abnormalities in the periosteum, costochondral junctions, and diaphysis. Congestion was found in the lower lobes of both lungs but there was no pneumonic exudate or hemorrhage. The duodenum was filled with a large fresh blood clot which originated from an ulcer on the posterior surface of the duodenum 2 cm. from the pylorus. The base of the ulcer lay in the head of the pancreas, was granular, and contained a small thrombus which was attached to an eroded blood vessel. Numerous leucocytes infiltrated the walls and base of the ulcer. The entire intestinal tract was filled with dark, gelatinous blood clots.

Brain.—Macroscopic examination of the brain revealed no abnormalities, but on histologic examination there appeared widespread changes in the cerebral cortex. Most extensively involved were the insular, occipital, and hippocampal gyri, which showed ischemic necrosis of the ganglion cells, sometimes involving one and sometimes all of the laminae. The third cortical layer, however, was most frequently destroyed. The same ischemic involvement of nerve cells was seen in the claustrum and pallidal nuclei. The cornu ammonis formations had lost all but a few cells of the Sommer's sector (Fig. 11). None of the nuclei in the medulla were injured.

CASE 9.—A white male infant, 6 months old, with history of intractable diarrhea from birth. There was respiratory difficulty, followed by cessation, requiring stimulants and artificial respiration. Death occurred after twelve hours. There was cerebral edema and destruction of nerve cells of the cerebral cortex associated with glial proliferation.

Clinical History.—The patient was a white 6-month-old male infant who began having five to seven loose green stools daily from the age of three days until his admission to the hospital, twenty-five days before death. The intractable diarrhea was seemingly uninfluenced by any methods of feeding, although these were repeatedly changed. The child was breast-fed during the first three months of life, then received breast and supplementary feedings for the next two months. At this time a series of experiments in feeding was begun by the mother, who changed the diet whenever she heard of some new food or when she suspected that the old was injuring the baby. The child was finally brought to the New Haven Hospital because of the diarrhea, extreme pallor, emaciation, and unexplained fever.

The birth of the child was said to have been normal and spontaneous. There were no convulsions or cyanosis. This was the first child of a 26-year-old mother who had no other pregnancies.

The diarrhea could not be controlled in the hospital, even when all food by mouth was stopped for a while and the child was given parenteral fluid, intravenous glucose, and transfusion. As soon as the food by mouth was increased above 30 calories per kilo, the diarrhea recurred. The temperature was elevated throughout the course, sometimes reaching 39° C.

At 8:30 one evening, the child developed Cheyne-Stokes respiration and became cyanotic. One hour later he suddenly ceased breathing entirely, and the heart sounds became very faint. Stimulants revived him somewhat, but the Cheyne-Stokes breath-

ing continued. Again one-half hour later the respirations ceased, necessitating artificial respiration. The child seemed then to have revived, although he remained cyanotic, but at nine o'clock the following morning he died.

Repeated blood cultures yielded no growth of organisms. The white blood cells were always above 14,000, and the differential count showed 73 per cent leucocytes and 23 per cent lymphocytes. The blood Kahn reaction was negative, as was also the tuberculin reaction.

Fig. 11.

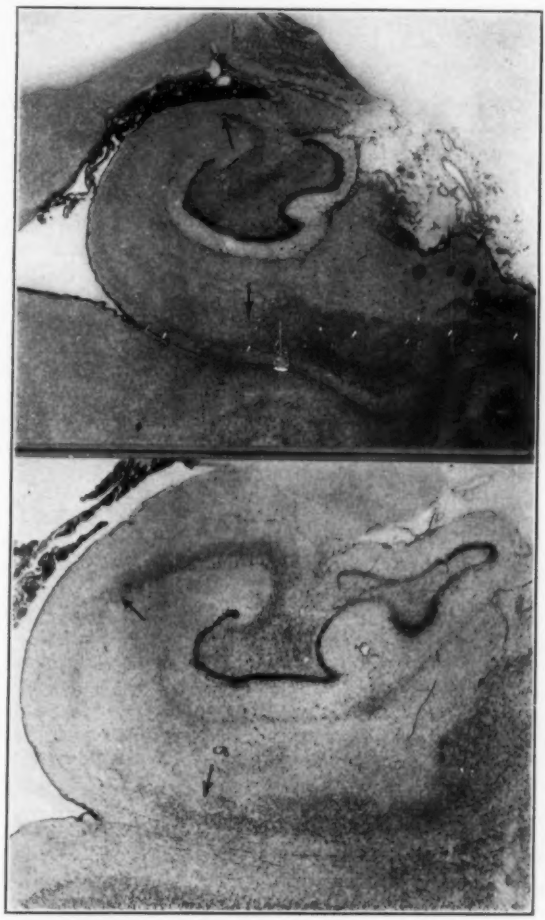

Fig. 12.

Fig. 11.—Case 8. There is a disappearance of all but a few nerve cells in Sommer's sector of the cornu ammonis formation. Nissl stain. (×11.)

Fig. 12.—Case 9. Part of Sommer's sector (between arrows) is devoid of ganglion cells. Nissl stain. (×18.)

Necropsy.—Necropsy was performed by Dr. Dan Egbert five hours post mortem. Aside from the lesions in the nervous system, the only positive findings were the emaciation and a fibrosis of the pancreas. The fibrous tissue in this organ was infiltrated with large numbers of lymphocytes.

Brain.—Macroscopic examination of the nervous system revealed no abnormalities. Histologically there was seen widespread cortical damage characterized by a diminution in the number of ganglion cells in the superficial laminae. This was associated with a proliferative response on the part of the glia, chiefly of the astrocytic variety. The chief damage had occurred in the cornu ammonis formations (Fig. 12), but the cortex of the frontal, parietal, and occipital lobes was also involved. The basal ganglions were spared.

Many of the nerve cells which still persisted were shrunken and hyperchromatic; others showed ischemic necrosis; some were surrounded by pericellular incrustations. There was evidence of edema throughout the brain, as manifested by greatly dilated perivascular spaces which imparted a spongy appearance to some portions.

CASE 10.—A 5-month-old white male infant was presumably well until sudden onset of illness with vomiting, drowsiness, and generalized convulsions. Respiratory difficulty and retinal hemorrhages culminated in death, in twenty-four hours. The infant had rickets and cerebral and subdural hemorrhages; there was destruction of nerve cells of the cerebral cortex.

Clinical History.—The patient, a white male infant, 5 months of age, was born to healthy parents following the first pregnancy, the course and termination of which were entirely normal. The child had been well until the onset of the present illness which started with forceful vomiting. He became increasingly drowsy, and there was generalized stiffening with twitchings of the right eye and the right hand. Breathing became stertorous, and the pupils were dilated.

On admission to the New Haven Hospital respirations were noted to be of the Cheyne-Stokes type. The skin was extremely pale, except for one small hemorrhagic nodule over the lower ribs in the right axillary line. Both fontanels were open and very tense. The pupils were dilated and fixed. The fundi, especially the right, showed a number of small fresh hemorrhages, and the right disk was obscured by a massive hemorrhage. The heart sounds were rapid and high-pitched. The blood pressure was 105 mm. of mercury systolic and 70 mm. diastolic. There was a positive Babinski sign on the left, but the deep reflexes were normal. Death occurred eighteen hours after admission to the hospital and about twenty-four hours after the first generalized convulsion.

Lumbar puncture revealed xanthochromic fluid with an initial pressure of 350 mm. of water. The rapidly fatal termination precluded any laboratory examinations.

Necropsy.—Post-mortem examination was performed by Dr. Lincoln Opper four and one-half hours after exitus.

The body was well nourished and well developed. The occipital and parietal bones of the calvarium were extremely soft to palpation. Small, sharply circumscribed fenestrations were found everywhere in the calvaria, which was peculiarly square-shaped due to the prominences of the frontal and parietal bosses. The lower ribs were flared in bell fashion. A microscopic preparation of an osteochondral junction of a rib showed a typically rachitic zone containing strands and clusters of large vesicular cartilage cells in place of osteoid tissue. This junction also showed an increased vascularity. There were no subperiosteal hemorrhages, but petechiae were found in the splenic capsule, thymus, and pleurae.

The liver was normal in size, weighing 205 gm., but it was mottled externally and on section with irregular green-yellow patches. Microscopically there was noted a diffuse hepatic fibrosis which was most marked in the periportal zones. Small round cells and plasma cells were seen in the proliferating connective tissue which replaced cords of liver cells. There was marked stasis in the bile capillaries.

Brain.—A large subdural hematoma of recent origin was present over the right parietal lobe. This appeared to arise from a massive hemorrhage in the right temporal lobe which ruptured through the superior temporal gyrus (Fig. 13). There

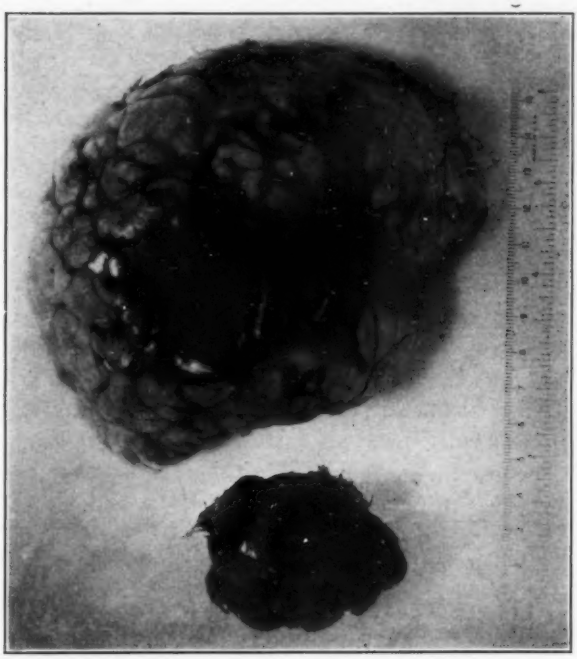

Fig. 13.—Case 10. Photograph of the brain showing the site of hemorrhage in the right temporoparietal region. The blood clot, which has been removed, lies below.

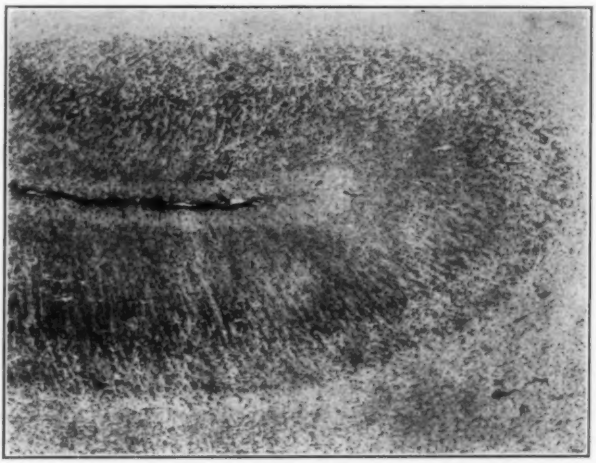

Fig. 14.—Case 10. The moth-eaten appearance of the cerebral cortex is due to necrobiosis of the ganglion cells. Nissl stain. (×25.)

was nothing to indicate the source of the hemorrhage either in the gross or on microscopic examination. It was of recent origin, as indicated by the well-preserved red blood cells of which it was composed. The remainder of the parenchyma of the temporal lobe contained numerous small petechiae.

Throughout the cortex of the cerebrum and particularly in the occipital lobes there were found foci of necrosis involving the ganglion cells. These foci had no predilection for any particular cortical layer, being so widely disseminated in all the layers as to impart a moth-eaten appearance to the cortical cytoarchitecture (Fig. 14). In most instances the cells had completely disappeared without leaving any trace. The glia cells did not participate in the reaction.

Comment.—Each of the three infants in this group had a severe grade of malnutrition to which the final illness, which was characterized by Cheyne-Stokes respiration or convulsive seizures, was attributable. In Case 9 only was there any fever, and this was due to dehydration. Acute infection was not a part of the clinical course in these children, yet the cerebral lesions demonstrated at necropsy were similar in kind and distribution to those found in the children who succumbed during acute infections. The cerebral edema in Case 9 and the hemorrhages in Case 10 were evidences of disturbed cerebral circulation resulting from respiratory difficulty or convulsions, having the same pathogenesis, therefore, as the necrobiotic lesions themselves.

CONVULSIONS FOLLOWING ICTERUS GRAVIS

CASE 11.—A white male child, 11 months old, who had icterus gravis neonatorum accompanied by generalized convulsions and followed by repeated spasmodic attacks and mental retardation, had a sudden onset of respiratory difficulty, resulting in death nine hours later. There was widespread destruction of nerve cells in the cerebral cortex, basal ganglions, and nuclei of the medulla and cerebellum.

Clinical History.—The patient, a white male child aged 11 months, was born by low forceps delivery following a normal pregnancy. There was no history of birth injury. At the age of 5 days he developed jaundice, which became very severe during the course of the next few days and was accompanied by convulsions. He remained in the hospital for six weeks, at the end of which time the jaundice had completely disappeared, and he was discharged.

At home he continued to have daily spasmodic attacks and appeared to be definitely retarded mentally. For this reason he was admitted to the New Haven Hospital where physical examination revealed a well-developed and well-nourished child who was spastic, apathetic, and out of touch with the environment. The head was held slightly retracted, though it could readily be flexed on the neck. The reflexes were hyperactive, and there was a questionable bilateral Babinski sign. Encephalography revealed a moderate increase in the size of both lateral ventricles and, to a lesser degree, of the third and fourth ventricles. There appeared to be some cortical atrophy.

Once more the child was discharged from the hospital to his home where his course remained uneventful until the day of death. On the morning of that day, at 11:30, he was apparently doing well, but at 12:10 he was found limp and cyanotic. He was not breathing, and his heart was not beating. At 12:20 adrenalin

was injected intracardially, and artificial respiration was started. The heart began to beat a few minutes later, and at 12:40 he gradually began to breathe. He remained limp and motionless until 2:30 P.M., when the muscle tonus gradually increased. The child became spastic and had a well-sustained ankle clonus. There were occasional twitchings of the jaw. At 9:20 P.M., he became cyanotic and died of respiratory failure without having regained consciousness since noon.

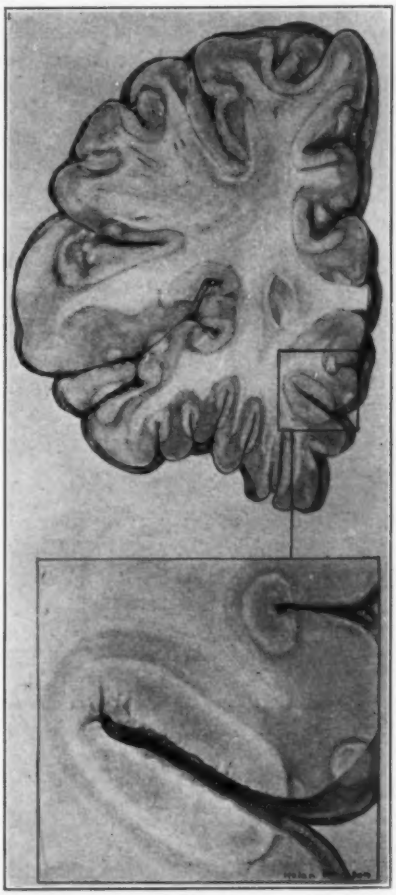

Fig. 15.—Case 11. Patches of discoloration due to necrobiosis are seen in the cortical gray matter in the troughs and at the sides of the sulci. Drawing of frontal lobe.

Necropsy.—Post-mortem examination, which was limited to the intracranial contents, was performed by Dr. David M. Grayzel one hour and twenty minutes after exitus.

Brain.—The brain was well developed, and there was no apparent atrophy of the cerebral convolutions. There was likewise no evidence of internal hydrocephalus. An amazing picture of yellow, patchy discoloration was seen in the cortical gray matter, occurring in the majority of instances in the troughs of the cerebral sulci

and extending occasionally along the sides of the sulci (Fig. 15). The lesions were sharply limited to the cortical gray matter and did not appear to extend to the subcortex. Similar discolorations were seen in the central gray matter, particularly in the thalami and putamina. The cortex of the occipital lobes showed the most extensive involvement.

On microscopic examination the cortex presented a moth-eaten appearance due to the disappearance in patches of many of the ganglion cells (Fig. 16). Sometimes this lesion involved one and sometimes another of the cortical laminae, but more often all six layers were involved. When one layer alone was destroyed, it was usually the third. The involvement was predominant in the depths of the cerebral sulci, but in rare instances the crests of the convolutions were also implicated. The lesions were more extensive in some of the gyri than in others. Thus the entire cornu ammonis formations were destroyed, and the cortex of the occipital lobes was much more extensively involved than the cortex of any other lobe. Similar

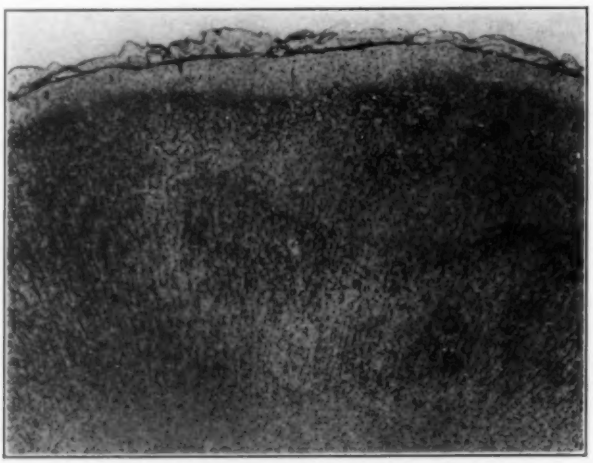

Fig. 16.—Case 11. The photomicrograph shows a peculiar ringlike, bleached zone in which there is necrobiosis of ganglion cells. Motor cortex. Nissl stain. (×25.)

lesions were present in the caudate nuclei, the putamina, the inferior olives of the medulla, and the dentate nuclei of the cerebellum.

The surviving nerve cells in the foci of injury were altered in a variety of ways. Often they were ischemic. Occasionally they showed hydropic degeneration and contained one or more vacuoles in their cytoplasm. Many of the cells were surrounded by pericellular spaces of edema. Chronic cell damage was found in almost every focal lesion. Some cells were shrunken and hyperchromatic, and there was a loss of distinct demarcation between nucleus and cytoplasm. Pericellular incrustations were found outside some of the cell bodies and their processes. The glia was not involved in either degenerative or proliferative responses. There was no evidence of bile pigments or bile salts in any part of the brain.

Comment.—This child undoubtedly had jaundiced basal ganglions during the course of the icterus gravis, for the lesions in the caudate nuclei, putamina, inferior olives, and dentate nuclei are the well-recog-

nized residua of this condition. The mental retardation and the spasticity likewise fit in with this assumption. The hyperchromic cell change and the more recent necrobiosis, however, are to be accounted for on the basis of the convulsive attacks during the neonatal period and the respiratory collapse during the final nine hours of life.

BIRTH INJURY AND ASPHYXIA

CASE 12.—A white female infant, 3 days old, born to 19-year-old primipara after moderately severe labor lasting 19 hours, was covered with meconium. Alternating periods of pallor and cyanosis were associated with irregular respiration. There were right facial paralysis, spasticity of the left arm, bilateral ankle clonus, and dissociation of ocular movements. There was destruction of nerve cells of cerebral cortex, associated with glial proliferation.

Clinical History.—The patient was a white female infant born to a 19-year-old primipara. Birth followed a nineteen-hour labor of moderate severity, and delivery was spontaneous. At birth the infant was covered with meconium and breathed poorly. Stimulants were administered and the baby was placed in a respirator when breathing became more regular. About six hours after birth a right facial paralysis was noted. Three times during the following morning the baby vomited tarry material, which gave a positive guaiac reaction. Periods of pallor alternating with periods of cyanosis were present.

The patient was pale and drowsy and had irregular, rapid, and deep respirations which alternated with periods of apnea and cyanosis. At times the eyes deviated to the left. The fundic veins were full, but there were no retinal hemorrhages. The mouth was pulled to the left, and there was right facial weakness. The left arm was held in flexion and was slightly spastic; the right was almost flaccid. Reflexes of the lower extremities were not abnormal, but there was a slight increase in the right knee jerk.

On the day following birth, a bilateral ankle clonus was noted. The anterior fontanel felt boardlike, but was not full. The next day complete dissociation of ocular movements appeared. An odor of acetone was detected on the breath, and a urine specimen at that time showed four-plus acetone, two-plus albumin, and one-plus sugar. In spite of clyses and gastric lavage, the child did not improve. The respirations became shallow, grunting, and irregular, and the fontanel bulged slightly. A few râles at the right base were noted, and the child vomited bloody material. Death occurred on the third day.

Bleeding time was three minutes, and clotting time was three minutes. Blood culture was positive for *Streptococcus hemolyticus*. Spinal, cisternal, and ventricular punctures were attempted without success.

Necropsy.—Post-mortem examination was performed by Dr. David Dial one hour after exitus, and the following is an abbreviated transcript of his protocol.

The body was well developed and appeared well nourished, measuring 51 cm. in length and weighing 3,450 gm. About 10 c.c. of clotted blood were present in the left thoracic cavity, and a smaller quantity was found in the pericardial sac. The lungs were mottled alternately with light and dark red patches of consolidation. These were most numerous in the lower lobes and showed, on microscopic examination, a pneumonic exudate of leucocytes, fibrin, and red blood cells. Amniotic material was not to be seen in either the bronchioles or the alveoli.

Brain and Spinal Cord.—The cerebral convolutions were distinctly flattened; otherwise there were no changes noted on macroscopic examination. Microscopically, the usual cortical cytoarchitecture was obliterated in large numbers of cerebral gyri (Figs. 17 and 18). Marked astrocytic proliferation was seen in the first cortical lamina; occasionally such cells were in mitotic division. In the deeper laminae, the rod-shaped Hortega cells were most numerous. The nerve cells of these layers, however, had completely disappeared. In a few isolated zones groups of nerve cells persisted uninjured in the midst of wide fields of cellular destruction.

Fig. 17.

Fig. 18.

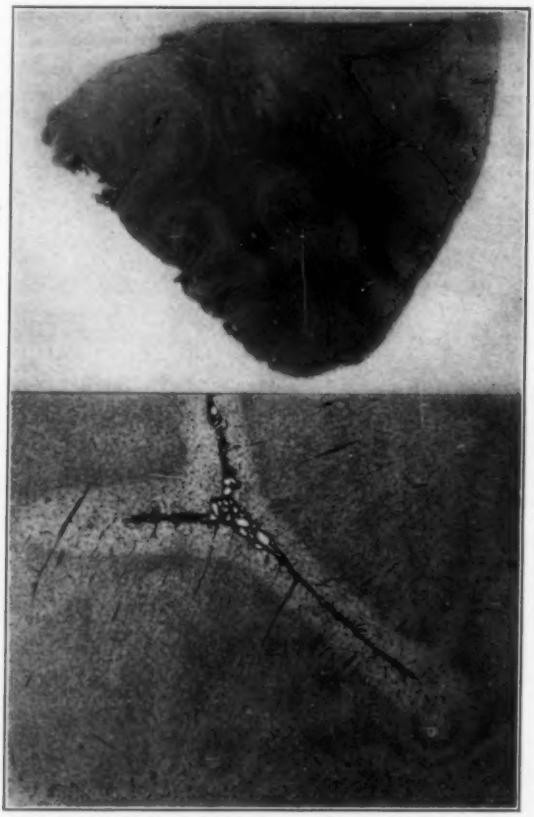

Fig. 17.—Case 12. Photomicrograph of part of the occipital lobe. The entire cortical cytoarchitecture is obliterated and there is a reversal of the staining properties, the subcortical white matter being stained darker than the cortical gray. Nissl stain. (×2.)

Fig. 18.—Case 12. The ganglion cells of the cortex of three adjacent gyri in the occipital lobe have completely disappeared. The glia has proliferated to a mild degree. Nissl stain. (×25.)

In the subcortical white matter the glial reaction was more widespread, more active, and more varied. Glia in mitotic division were more frequently encountered here than in the cortex. Phagocytic cells filled with fat were present in abundance, and there was evidence to indicate that some of the myelinated fibers were undergoing destruction.

In several places in the centrum ovale as well as in the reticular formation of the pons, several small hemorrhages were found, in which the red blood cells had become laked and had liberated their pigment.

CASE 13.—A black male infant, 3 days old, was born to 16-year-old primipara after induced labor in the eighth month of gestation. He was apparently normal

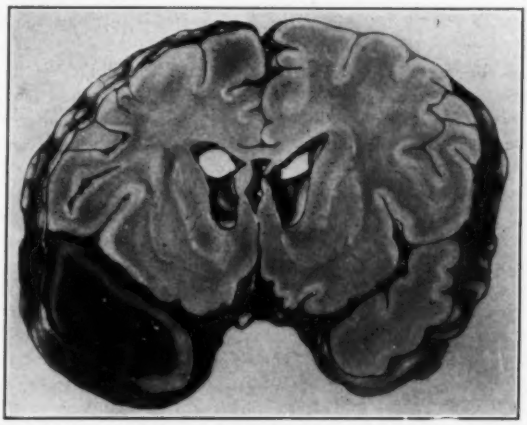

Fig. 19.—Case 13. Drawing of a section of the brain to show the hemorrhage in the right temporal lobe.

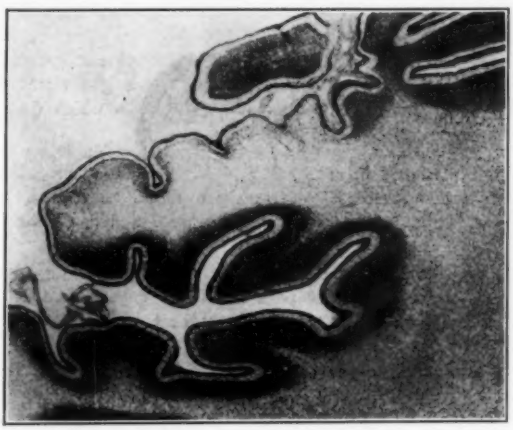

Fig. 20.—Case 13. The Purkinje and granular cells of several lobules of the cerebellum have disappeared. Nissl stain. (×25.)

until five hours preceding death, when feebleness, respiratory difficulty, facial weakness, and retraction of the head were noted. There were massive intracerebral and subarachnoid hemorrhages; nerve cells of the cerebral and cerebellar cortex were destroyed.

Clinical History.—The patient was a 3-day-old black male infant born to a primipara who was 16 years of age. Roentgen-ray pelvimetry revealed a small pelvis

in the mother and a large fetus, consequently it was considered advisable to induce labor in the eighth month of gestation. Quinine and castor oil were used without effect. Finally, pitocin was employed intranasally, and pains began. The delivery was normal and spontaneous and the child cried well following delivery. First stage of labor lasted seventeen hours and second stage, forty-five minutes.

For the next three days the child seemed to be doing well. His birth weight was 3,360 gm., and he lost only 235 gm. He was nursing poorly, but the mother had not begun to lactate well. Temperature and respiration were normal. There were no restlessness, irritability, or convulsions.

At midnight of the third day he appeared feeble and seemed unable to grasp the nipple when put to breast. Four hours later the respirations became very irregular, and the color was poor. A questionable facial weakness was noted, but there were no convulsions. The head was retracted and the fontanel was full. Supportive treatment was without avail, and the child died one hour later.

The Wassermann reaction on the mother's blood was negative.

Necropsy.—Post-mortem examination was performed by Dr. John Mendillo six hours after exitus. The findings other than those in the nervous system were not contributory.

Brain.—A massive subarachnoid hemorrhage, which had its origin in the underlying parenchyma, covered the entire right temporal lobe (Fig. 19). Hemorrhage was also found in both sylvian fissures and over the orbital surfaces of the frontal lobes. A large blood clot was found in the right cerebellar lobe, which compressed the pons and in part destroyed the vermis cerebelli. The lateral ventricles were dilated as the result of the compression of both the aqueduct of Sylvius and the fourth ventricle. Clotted blood was found in the right lateral and in the third ventricles.

In several places near the sites of the parenchymal hemorrhages, greatly dilated blood vessels with thin walls were encountered, which were markedly congested. It appeared that some of these, by rupturing, had produced the extensive hemorrhages. The cerebral cortex was the seat of widespread destruction of ganglion cells. These cells alone had been injured and had disappeared; the glia remained intact. The cerebellar cortex also contained small zones of necrosis which destroyed Purkinje cells and the small granular cells (Fig. 20).

CASE 14.—A white male infant, 2 days old, was born after induced labor when fetal movements nearly ceased. He was pale, cyanotic, anemic, and had respiratory difficulty. There was a true knot in umbilical cord and destruction of nerve cells of the cerebral cortex.

Clinical History.—The patient was a white male infant, 2 days of age, who was born at full term to a 35-year-old para ii. Three days before delivery, the fetal movements became less marked, but the heart beat was audible in the left lower quadrant and was strong and regular. Labor was induced with castor oil and quinine, and pains started after several hours. The descent of the head was slow so that low forceps were employed.

At birth the infant was pale and cyanotic, and although the lungs were well expanded, there was a low respiratory grunt. A true knot was found in the cord when the placenta was delivered, but the placenta itself appeared to be normal. The infant had a blood count of 2,700,000 red blood cells and 50 per cent hemoglobin. Because of this, he was transfused with 80 c.c. of the mother's blood, to which he reacted well. Without showing any untoward signs, he expired on the second day of life.

Necropsy.—Post-mortem examination was performed by Dr. Knox H. Finley eight hours after exitus. The necropsy revealed no unusual findings except in the nervous system.

Brain.—On macroscopic examination there could be seen no abnormalities in the meninges and cerebral parenchyma. Microscopically, both the parietal and occipital cortex contained large zones in which there was an almost complete absence of the ganglion cells in the third, fourth, fifth, and sixth layers (Fig. 21). The second layer was nearly normally preserved. Those ganglion cells which still persisted in the involved zones showed a loss of the Nissl bodies and indistinctness of the nuclei. The glia was altered by a degenerative change somewhat similar to that in the nerve cells; the nuclei were shrunken, irregular, and granular.

CASE 15.—An 18-month-old white male child, born after instrumental delivery, had a convulsion lasting ten minutes on third day of life. Well until the onset of irritability, there were repeated convulsions, vomiting, and loss of consciousness, which resulted in death at the end of twenty-four hours. There was destruction of nerve cells of the cerebral cortex.

Clinical History.—The patient was a white male infant, 18 months of age, who was born following a labor of four hours which was terminated with the aid of

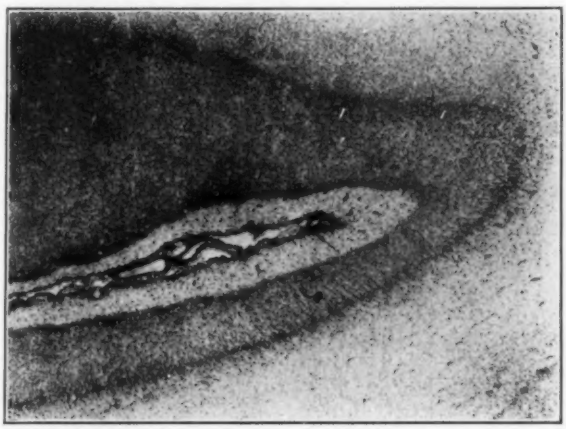

Fig. 21.—Case 14. The cortical cytoarchitecture of the occipital lobe is blurred as the result of extensive necrobiosis of the ganglion cells. Nissl stain. (×25.)

forceps. The birth weight was 9 pounds, 4 ounces. The infant cried well following delivery and appeared to be perfectly well until the third day, when he had a generalized convulsion lasting ten minutes. From this he recovered without apparent ill effects and developed normally, sitting up at 4 months and walking at 12 months. Teething started when the child was 5 months old and just beginning to talk.

The illness had its beginning one evening when the child accidentally struck his head several times on a carpeted floor. He picked himself up on each occasion but appeared slightly dizzy. At bed time, two hours later, he appeared somewhat irritable but fell asleep fairly promptly. Early the following morning the child became very irritable and cried considerably. His eyes rolled upward, and the mother thought he was having a convulsion. Following this he had a peculiar "stare," and it was noted that he was unconscious. Before his admission to the New Haven Hospital he had a series of twenty convulsions spaced about twenty minutes apart, each convulsion lasting about five seconds. The legs and arms were in flexion. The child vomited frequently. The temperature was normal throughout.

On admission to the hospital, the child was still unconscious. He had a convulsion which was characterized by a turning of the head to the left and extension of the feet and legs, with the toes assuming a fanlike position; the arms were flexed and the eyes turned upward. The Babinski sign was positive bilaterally.

A bilateral subtemporal decompression was made soon after admission in view of the history of repeated head trauma. Nothing was found. Following the operations the convulsions ceased, but the child still did not regain consciousness. Three hours later the respirations became labored and finally stopped, twenty-four hours after the onset of the illness.

Lumbar puncture revealed an initial spinal fluid pressure of 250 mm. of water, which rose to 300 mm. when the child was crying. The fluid was clear and contained but two cells and no albumin. Blood culture yielded negative results. The blood Kahn test was negative.

Necropsy.—Post-mortem examination, which was limited to the intracranial contents, was performed by Dr. Knox H. Finley five hours after exitus.

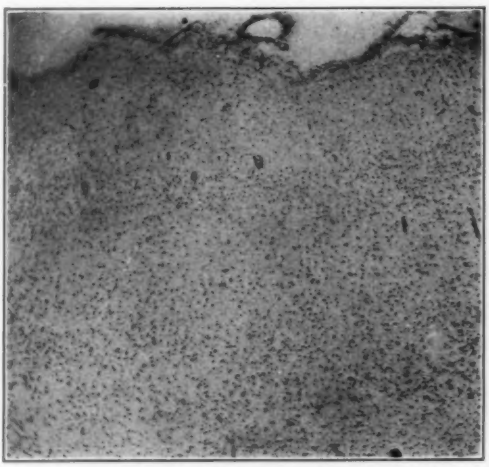

Fig. 22.—Case 15. The bleached appearance of the cerebral cortex is due to necrobiosis of the ganglion cells. Nissl stain. (×40.)

The defects in the parietal bones, which were made during the craniotomy procedures, each measured 2 cm. in diameter. There was no evidence of subdural hemorrhage. The leptomeninges were pale and translucent everywhere. Macroscopic examination of the brain revealed normal structures.

On histologic examination nearly all the ganglion cells of the cerebral cortex appeared swollen and lacked Nissl granules. Their nuclei were shrunken and hyperchromic and failed to show nucleoli. In some gyri the nerve cells had completely disappeared, altering to a marked degree the laminar appearance of the cortex (Fig. 22). To a less degree these same cellular changes were present in the basal ganglions, pons, and cerebellum.

Comment.—The histories of birth injury or asphyxia cannot be disputed in Cases 12, 13 and 14, and the pathogenesis of the cerebral lesions is, therefore, a matter of simple deduction. These cases are of the utmost importance in illucidating the pathogenesis of the lesions in

all the other cases. There is only presumptive evidence that the child described as Case 15 suffered a birth injury, this evidence consisting of the facts that the child was large at birth, was delivered by forceps, and had a severe generalized convulsion on the third day of life. There can be no doubt, however, that the cerebral lesions found on post-mortem examination had resulted from the repeated convulsions which occurred during the final twenty-four hours of life. Unfortunately, a partial examination precluded the discovery of the cause of these convulsions and the widespread distribution of the recent cerebral changes could have obscured any older lesions.

PNEUMOTHORAX WITH PARTIAL ASPHYXIA

CASE 16.—A 6-month-old white female child developed neurogenic fibrosarcoma in left kidney region. There was surgical shock and left pneumothorax following operative removal of tumor. The pulse rate was rapid and feeble, and respirations, slow

Fig. 23.—Case 16. Photomicrograph of occipital cortex showing faded appearance of several gyri due to necrobiosis. Nissl stain. (×2.)

and shallow. There were twitches of the right arm and lips. Large and petechial hemorrhages were scattered in the brain; there was destruction of nerve cells in the cerebral cortex.

Clinical History.—The patient was a white female child, 6 months of age, who was born following high forceps delivery after about one-half hour of labor. The membranes had ruptured three hours previously. The child appeared normal at birth and had a normal feeding and developmental history.

In the course of a routine physical examination at 3 months of age, the child was found to have a firm mass in the left upper quadrant of the abdomen. This was found to be a renal tumor, and after a course of deep roentgen-ray therapy it was decided to perform a nephrectomy. Accordingly, under ethylene and ether anesthesia the left kidney and adrenal were removed together with the adherent spleen and a portion of the pancreas. During the course of the dissection the left costophrenic sinus was cut, and although the rent in the pleura was immediately sutured, the patient went into "surgical shock." The heart shifted to the right. A

needle was inserted into the left pleural cavity at the seventh interspace and 75 c.c. of air were removed. The child grew worse; the pulse rate rose to 200 per minute; the respirations became slow and shallow. Slight twitches of the right arm and lips occurred, and the child expired approximately thirty hours after the operation.

Examination of the tumor revealed a fibrosarcoma of neurogenic origin.

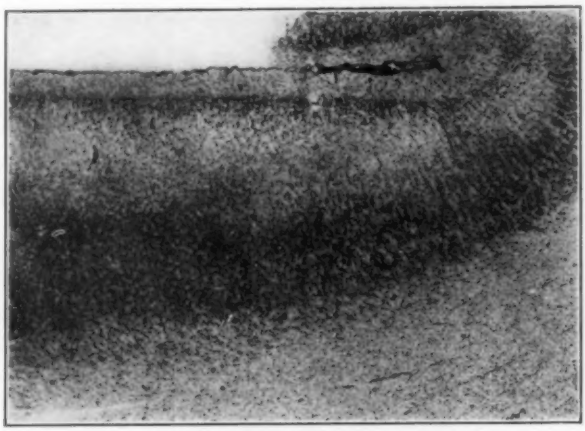

Fig. 24.—Case 16. The ganglion cells of the cortical layers, especially the third, have completely disappeared. Nissl stain. (×25.)

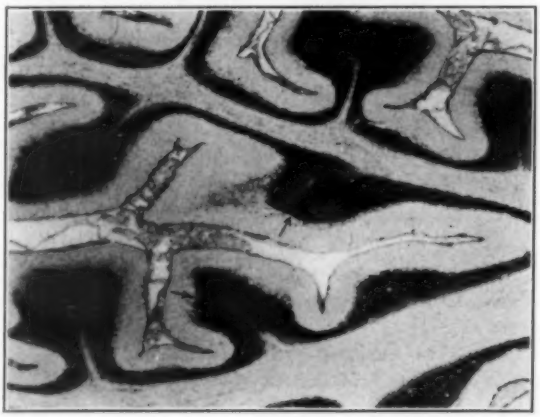

Fig. 25.—Case 16. Photomicrograph of cerebellar cortex. Note faded appearance of the granular cell layer due to necrobiosis. Nissl stain. (×25.)

Necropsy.—The necropsy was performed by Dr. David M. Grayzel one and one-half hours post mortem. Aside from the evidence of the recent surgical procedure, the important findings were confined to the nervous system.

Brain.—A small fresh blood clot was seen in the subdural space between the two cerebral hemispheres. A focus of hemorrhagic discoloration measuring 8 mm. in diameter was present in the cortex of the left occipital lobe at the base of one

of the sulci. This had the appearance of an hemorrhagic infarct and represented the only macroscopic abnormality noted in the entire brain.

In addition to the hemorrhage in the left occipital lobe, microscopic examination revealed numerous petechiae and congested vessels in other parts of the brain. In many places the cerebral cortex had lost its nerve cell elements, this lesion being confined to the third layer in some gyri and involving all the layers in other gyri (Fig. 23). The necrobiosis had a pseudolaminary distribution, especially in the occipital lobe cortex (Fig. 24). A moth-eaten appearance was presented by the cerebellar cortex where the granular cells had a faded appearance in the Nissl preparations (Fig. 25). The Purkinje cells were either entirely absent in circumscribed zones or were swollen, round, and vesicular.

Comment.—In no case of this whole series is the pathogenesis of the cerebral injury more certain than in this one. The pulmonary collapse designated as "surgical shock," with its attendant respiratory failure and cerebral ischemia, accounts for the histologic lesions, which are clear-cut and in every way comparable to those in the other cases.

GENERAL COMMENT

Analysis of the clinical histories and histopathologic changes in the nervous systems of this group of children, which succumbed to severe convulsive disorders, respiratory failure, or asphyxia, leads to the conclusion that the lesions resulted from cerebral anoxemia. This point of view is in agreement with that expressed by Spielmeyer and his school. Little need be added in explanation of the method by which cerebral anoxemia is produced as the result of respiratory collapse or asphyxia. Nor is it particularly difficult to understand how the ganglion cells, which are peculiarly susceptible to anoxemia, are injured, especially in young children. It is not as readily understood how convulsive attacks produce the anoxemia.

As already mentioned, Spielmeyer felt that cerebral angiospasm in many instances preceded or accompanied the convulsion. This could readily produce anoxemia, but the proof for such a mechanism is difficult to deduce from necropsies. In our cases it appears rather that the convulsive attacks, which were associated with great respiratory distress, produced venous stasis in the brain as the result of increased intrathoracic pressure, and this led to cerebral anoxemia.

This paper does not deal with the pathogenesis of convulsions, but rather with the histopathologic changes which these produce in the nervous system. The changes are to be regarded solely as the result of the convulsive attacks; it is not conceivable that they were preexisting and initiated the attacks. It must be emphasized that in no instance in this series was an encephalitis responsible for them.

SUMMARY

Extensive necrobiotic changes of the ganglion cells were found in the cerebral cortex, especially the cornu ammonis formations of the temporal lobes, the basal ganglions, and the cerebellar cortex of a group of

sixteen children ranging in age from early infancy to 6½ years. The lesions were similar to those described by Spielmeyer and others in cases of epilepsy. Severe convulsions and prolonged periods of respiratory difficulty or asphyxia dominated the clinical pictures in these cases. Although seven of the children had an underlying infectious illness which suggested the possibility of encephalitis as the cause of the symptoms, the other nine were free from infection. None of the children had inflammatory cerebral lesions which could have accounted for the symptoms. It was concluded that cerebral anoxemia, resulting either from the convulsions, the respiratory difficulty, or the asphyxia, was responsible for the lesions in the nervous systems.

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NICOTINIC ACID IN THE TREATMENT OF ACRODYNIA

FREDERICK F. TISDALL, M.D., F.R.C.P.(C.), T. G. H. DRAKE, M.B., F.R.C.P.(C.), AND ALAN BROWN, M.D., F.R.C.P.(C.)
TORONTO, ONT.

IN SEPTEMBER, 1937, Elvehjem et al.[1] reported the cure of black tongue in dogs by the administration of nicotinic acid. For many years it has been known that black tongue in the dog and pellagra in the human being respond favorably to the same dietary procedures. Following this lead, Spies et al.[2] and Fouts et al.[3] in November, 1937, and later others, reported spectacular results in the treatment of pellagra with nicotinic acid. Thus a chemical compound known for some seventy-five years has now been shown to be essential for human nutrition.

Although acrodynia and pellagra are distinct clinical entities, there is a superficial resemblance between the two diseases. They both have skin lesions and they both may have involvement of the mucous membranes of the mouth. Until the discovery of the role of nicotinic acid in pellagra, they both responded very slowly to dietary or other therapeutic procedures.

The etiological factors in the development of acrodynia are unknown. In view of the similarity of the symptoms of acrodynia and those which can be produced in animals by dietary deficiencies, one view is held that acrodynia is due to a defect in the utilization by infants and children of some essential food element, probably belonging to the vitamin B complex. Another widely held view is that acrodynia is a particular and unusual response to a toxemia, as practically all these children have evidence of throat infection with involvement of the tonsils. These two views, however, can be reconciled. On one hand it is recognized that almost any dietary deficiency results in a lowered resistance to infection; therefore, these children would be more susceptible to infection than the average child. On the other hand, the presence of an infection interferes with the utilization by the body of many of the nutritional factors, including members of the vitamin B complex.

In view of these facts, an attempt was made to determine whether nicotinic acid, now known to be a member of the vitamin B complex, is of value in the treatment of acrodynia. Accordingly, the acid was administered to six infants suffering from this disease. Their ages were 8, 11, 12, 12, 17, and 24 months. They all had typical symptoms of acrodynia, namely, marked irritability, loss of appetite, rash and redness of the skin, the redness involving particularly the hands and feet,

From the Hospital for Sick Children, Toronto, and the Department of Paediatrics, University of Toronto.

later desquamation of the skin of the hands and feet, increased perspiration, so that the skin had the typical damp clammy feel, redness of the end of the nose, photophobia, and in the more severe cases redness of the gums and mucous membranes, with exfoliation of some of the teeth. In every instance there was redness of the pharnyx and involvement of the tonsils.

The nicotinic acid used was kindly furnished by Dr. Nielsen of the Abbott Laboratories. Two forms were used, pure nicotinic acid and the monoethanolamine salt of nicotinic acid. No difference was found in the action of these two substances. In regard to dosage, the only information we had to go on was Spies' experience that he was able to administer 500 mg. daily to adults, in five divided doses. In order to obviate any possibility of defective absorption from the intestinal tract, we gave the nicotinic acid intravenously by means of a continuous intravenous injection of a solution of one part normal saline and two parts 5 per cent glucose. The initial dosage was 20 mg., given over a period of about twelve hours. The method of administration was then changed to intramuscular injections, which were given twice daily the first day, 20 mg. each time, then the dose increased to 40 mg. twice a day. No local reaction occurred. In one or two instances the babies developed a definite skin reaction a short time after the injection. The skin became red and blotchy, but this passed off in the course of half an hour. In other instances, the infants were given the nicotinic acid by mouth, a total of 100 mg. a day being given to the younger infants, and 125 mg. a day to the older ones. The daily amount was given in three divided doses. Only occasionally was nicotinic acid found in the urine.

In view of the severity of the symptoms in most of the cases and the seriousness of the disease, we did not feel justified in eliminating the ordinary therapeutic procedures which in the past had been found to give the best results. Accordingly, all these infants, in addition to the nicotinic acid, received a diet which included milk, egg yolk, a mixture of equal parts of Pablum, wheat germ, and a finely ground green oat grass very rich in the vitamin B complex, oleum percomorphum, orange juice, and, in the older infants, liver. After the infants had been observed for a time, the tonsils and adenoids were removed.

With the first infant to receive the nicotinic acid, the photophobia largely disappeared in twenty-four hours. In the other cases, we could detect no evidence of any effect on photophobia. With the second infant, the rash dried up comparatively rapidly and at the end of four or five days had largely disappeared from the body; and the hands and feet instead of being a cyanotic, reddish color, became a light brick red, with the skin dry and starting to desquamate. At the end of two weeks the redness was barely perceptible. We gained the impression in practically every instance that the skin lesions tended to dry up and the skin to desquamate somewhat more quickly than we had observed without the

use of nicotinic acid. However, in one case the redness of the hands and feet returned during an exacerbation of the throat infection, although the infant was receiving 100 mg. of nicotinic acid daily. The mouth lesions did not heal any quicker than ordinarily. The rate of improvement of the infants was very slow, being interrupted at intervals by exacerbations of the nasopharyngitis, which evidenced itself not only by the redness of the nasopharynx but by irritability of the infant and almost complete loss of appetite, so that all feedings had to be forced.

It was evident that the nicotinic acid had no demonstrable effect on the clinical course of the disease as a whole.

CONCLUSIONS

Although nicotinic acid when combined with the therapeutic procedures usually employed in this clinic in the treatment of acrodynia seemed to hasten the healing of the skin lesions, no evidence was found that it shortened the period of recovery from the disease.

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INJURY OF THE CHILD BY ROENTGEN RAY DURING PREGNANCY

Report of a Case

F. Elmer Johnson, M.D.
New York, N. Y.

IN THE neurological and gynecologic literature many requests have been made for additional reports of infants born with abnormalities following irradiation of the fetus in utero. I shall report a case complete with details of dosage of roentgen ray and necropsy to add to the growing list. I am further motivated because the pediatric literature, including textbooks, pays so little attention to radiogenic anomalies.

Driessen[1] demonstrated in 1924 with experiments on rabbits that with exposure of one-half of the uterus to roentgen ray, the pregnancy on that side was terminated while the ovum on the other side continued to develop unmolested. This suggested to him that the effect of the radiation is a direct action on the ovum and cannot be ascribed to injury of the ovary. The earlier in pregnancy the radiation is given and the greater the intensity of the exposure the more the fetus is injured. Driessen concluded that exposures to radium or roentgen ray in the first half of pregnancy cause retrogression while those in the later half do not terminate pregnancy, but the newborn infants are subnormal in some way. The malformations are most liable to occur in the central nervous system, eyes, and blood vessels.

Murphy[2] in 1929 reported fifty-three women who received postconception radiation. Twenty-three of these aborted, but the others who went to term gave birth to children who were unhealthy according to the definition arbitrarily determined upon for the purposes of his study. Most of the pregnancies were unsuspected at the time of treatment. These defects were: underweight at birth, microcephalus, blindness, hydrocephalus, Mongolian idiocy, and other gross defects of structure and function, the majority of them involving the central nervous system.

Goldstein and Murphy,[3] in 1929, reported the results of a questionnaire sent to 1700 gynecologists and radiologists throughout the United States. With those found in the literature, they collected 106 case reports of women who had received radiation therapy during pregnancy. Seventy-four of these women were delivered of full-term children, but thirty-eight of the children presented disturbances of health or development of more or less serious nature. There was a high incidence of grave mental and gross anatomic defects. Sixteen were microcephalic idiots. The authors reported one patient of their own with micro-

cephalic idiocy born to a mother irradiated for carcinoma of the cervix late in pregnancy. They mention a similar case of Petenyi's born after roentgen ray therapy for carcinoma in the fifth and sixth months of pregnancy. Goldstein and Murphy conclude that no pregnancy should be allowed to continue to term when radium or roentgen ray therapy has been employed on the pregnant uterus.

Goldstein,[4] in 1930, published a paper which is more germane to our discussion in which he coined the term "radiogenic microcephaly." In this paper he dealt with nineteen microcephalic out of seventy-six infants born to mothers who were irradiated during pregnancy (25 per cent). He stressed particularly the ocular defects associated with microcephalus which occurred in a large number of these children. In many he observed disturbances of the eye ranging from abnormalities to inflammatory conditions. He suggested that some of these malformations, notably the microphthalmia, might be pathognomonic of radiogenic microcephalus. Heredity, syphilis, the previous general health of the mother prior to and during pregnancy, and the circumstances incident to labor were among the conditions studied. The cause of microcephalus in sixteen cases in this series could not in any way be ascribed to these factors.

Goldstein also found that the mothers had received relatively large doses, thirteen receiving more than one dose. Seven of the latter were given three or more treatments with a maximum in one case of seventeen. Sixteen were treated with roentgen ray, two with radium, and one with mesothorium. In general, pregnancy was unsuspected when the treatment was given. Ten were irradiated for myomas, three for carcinomas, two for sterilization, and four for miscellaneous reasons.

Of the fourteen children whose weight at birth was known, all but one were decidedly small, and four were premature. The head varied in shape and was small where measurements were recorded. The typical small round head of microcephalous infants occurred in nine. Three were oxycephalic, the type of head also known as "tower head" or "turmschaedel" and four children had flattened occiputs.

In fifteen children in whom the condition of the eyes was recorded, twelve had pathologic lesions. Although microphthalmia is found only once in 300,000 births in the general population, it was present in seven of these infants. In fifteen exposed to radiation in the first four months of gestation, eleven (73.3 per cent) manifested disturbances of the eyes. Only one of the other four irradiated after the fourth month showed an ocular defect. Defects other than neurological and ocular were not encountered consistently enough to classify. All of the children who lived were later classed as imbeciles or idiots.

Goldstein in his article compiled a table entitled, "Recorded Experiments Showing Irradiation Effects on Nervous System and Eyes." In four of the ten articles abstracted, by Bagg,[5] Hanson,[6] Hippel and Pagenstecker,[7] and Tribondeau and Belley,[8] microphthalmia was pro-

duced quite regularly in the offspring when their mothers were irradiated. Goldstein summarized the experiments as follows: "The intimate etiologic relationship between embryonal irradiation and developmental anomalies in the visual organs is further exemplified by observations made on the eyes of animals irradiated in utero and of young animals irradiated after birth. It is my belief that the method of irradiation employed experimentally in the pregnant animal or in the newborn offspring is comparable with the therapeutic method employed in the pregnant woman, especially as the types of defects observed clinically are similar to those observed experimentally. The table shows that optic atrophy and microphthalmia were produced in the young animal receiving irradiation of the eyes, and that, in experimental studies, cataracts were observed in the offspring of animals irradiated during pregnancy.

"The experimental studies recorded in the table demonstrate conclusively the facility with which serious diseases of the eye may be produced in young animals, either by maternal irradiation during gestation or by direct treatment of the head or eyes after birth. The eyes of the young animals and the embryonal optic anlage, therefore, appear to be very sensitive to irradiation. If fetal irradiation and irradiation of the eyes of the animal shortly after birth may be assumed to correspond with the irradiation received by the human embryo, it is obvious that the developing optic apparatus is especially sensitive to the injurious influence of radiant energy. This would account for the frequent occurrence of congenital microphthalmia, optic atrophy, and amaurosis in children with radiogenic microcephaly, particularly since nonradiogenic microcephaly is not associated with these types of defects of the eyes."

Goldstein and Wexler[9] have noted the constancy with which rosettes occurred in the retinas of the eyes of human embryos when large doses of roentgen rays were applied to the uterus during the first two months of pregnancy. The ciliary body and iris were also found to be rudimentary. They summarize by stating that the effect is stimulation or proliferation of the posterior segment, and inhibition or retardation of the growth in the anterior segment of the globe. The time of exposure in relation to the development determines the defect.

Ernest Farber,[10] in 1933, brought up to date the general conclusion of gynecologists on the effects of roentgen ray to the germ cells and fetus as follows:

"Roentgen irradiation of the ovaries does not seem to prevent the birth of a healthy child. However, irradiation of the pregnant uterus causes severe injury of the fetus, at least if it is done in the first months of pregnancy. In 50 per cent of the cases the injury consists in what Zappert calls 'roentgenogenic fetal microcephalia' associated with severe malformations of the eyes, the same as observed in the animal experiments. The effect of irradiation on the fetus when other organs of the pregnant woman are exposed may or may not affect the fetus." Farber,

however, mentions seven cases reported from the literature by Scholl in which microcephalus and eye defects occurred in children born of mothers irradiated for cancer of the breast, sarcoma of the thigh, etc. Farber also reports a case of his own which deserves reporting here. A woman was irradiated for cervical adenitis. She was amenorrheic during the entire treatment. She had often missed her menses before and being 30 years old and married eight years without children had not suspected that she was pregnant. She received ten treatments in three months, allegedly with the body shielded up to the breast. Increasing indisposition following the treatments was believed to be roentgen toxemia. The diagnosis of pregnancy was made soon afterwards. The baby was born six months later and weighed 2,600 gm. There was microphthalmia, complete coloboma, and at 21 months of age the baby was very backward mentally and physically. He concluded that "in any case the greatest precaution is indicated in irradiating sexually mature women who may possibly be pregnant not only when an irradiation of the uterus is intended but also for general and remote local irradiations."

Miller et al.,[11] in the latest article available, give the following summary quoted in part:

"It seems reasonable to advise that the use of radium and x-ray during pregnancy for treatment purposes be restricted to very clear and urgent indications and that the use of diagnostic x-ray examinations be not too frequently repeated during pregnancy.

"It seems advisable to interrupt any pregnancy which has been subjected to therapeutic radiation, for it is generally admitted that serious radiation effects on the offspring will result in a high percentage of cases. These effects are proportioned to the amount of radiation and are more serious in early pregnancies, though the fetus may be seriously injured at any stage of development."

CASE REPORT

A male infant, 6½ months old, was admitted to St. Luke's Hospital, New York City, on July 23, 1934. He weighed 2700 gm. at birth and had gained only 420 gm. He had always been weak, and the mother had noticed that his head was peculiarly shaped. For three days previous to admission he had vomited everything eaten. He had been fed since birth on the breast and supplementary cow's milk formulas. There was nothing abnormal about his birth history or in the examination of the alimentary tract.

The mother had had nine pregnancies. The first and eighth were miscarriages. The fourth pregnancy resulted in twins, one of whom died at 6 months of age with convulsions. The other children are well. Both parents had been treated for syphilis since 1927, and Wassermann tests on parents and baby on admission were negative. The parents were symptom-free at time of infant's admission.

In January, 1933, the mother visited a gynecologic clinic and was advised to have radiotherapy for fibroids of the uterus but was not treated until the following September. She was treated three times in fifteen days, receiving 1150 roentgen units in air. In utero it was estimated that the mother received 400 roentgen units. Later in November an Aschheim-Zondek test was positive for

pregnancy. The baby was born June 8, 1934, at full term. It was estimated that the treatments were given approximately seventeen, twenty-four, and thirty-two days after conception.

Upon examination the baby was found to be feeble although he had a fairly good cry. He preferred to lie on his side with his head retracted, arms flexed on chest and legs crossed. The head was relatively large, measuring 38.2 cm., while the chest was 33 cm. in circumference. The anterior fontanel measured 4 cm. longitudinally, and the tension was increased. The posterior fontanel was open, and the sutures were slightly separated. The eyes were small showing the sclera above the cornea. The pupils were dilated and eccentric with very little iris showing on the nasal side. The corneas measured only 6 mm. There was continual slow lateral nystagmus. The fundi were negative. The extremities were stiff, and the deep reflexes were increased. The infant's head was easily transilluminated.

Fig. 1.—Picture of child, showing microphthalmia and shape of head.

Repeated spinal punctures were done and, when the baby was not crying, showed a maximum pressure of 24 mm. of mercury. Examination of the fluid was negative.

Because of the translucency and shape of the head, a needle was inserted through the external horn of the anterior fontanel and 350 c.c. of fluid withdrawn and replaced with 350 c.c. of air. Roentgenograms were taken showing an external hydrocephalus and a small brain (Fig. 2). The needle wound continued to drain, and an infection of the meninges with *Staphylococcus aureus* resulted.

The salient features of the necropsy are in the examination of the head. Necropsy was done by Dr. Leila C. Knox. On opening the skull about 50 c.c. of yellowish flocculent fluid was found free about the brain surface beneath the dura. The brain was small and only filled the lower half of the entire cranial vault. It measured 28 cm. in its occipitofrontal circumference and weighed 225 gm. The pia and arachnoid, covering the entire surface of both hemispheres, were covered by a thick purulent, yellowish-white, foul-smelling exudate. This extended beneath the tentorium and to a lesser extent across the pons and medulla. Both cerebral cortices were flattened over their superior surfaces; their convolutions were small

and poorly demarcated. The frontal lobes showed marked agenesis, their anterior tips extending only 1 cm. beyond the anterior end of the temporal lobes. The sylvian fissures were poorly demarcated. The corpus callosum was rudimentary; the fornix and mammillary bodies were absent. On section the anterior and temporal horns of the lateral ventricles were narrowed and flattened; the occipital horns were somewhat dilated. Their ependymal lining was covered with soft, reddish, granular exudate. The choroid plexus of the lateral, third, and fourth ventricles was friable and showed severe inflammatory changes. The third ventricle

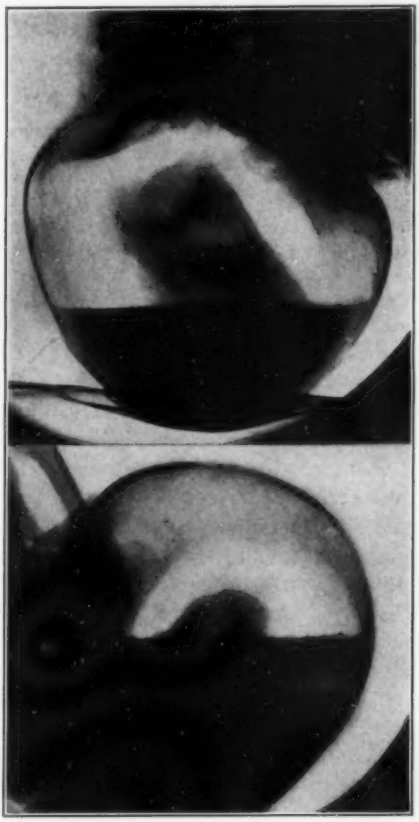

Fig. 2.—Roentgenograms of the head after displacement of spinal fluid with air, showing external hydrocephalus and small brain.

was very indistinctly defined, being a mere slit between the poorly developed optic thalami, posterior portion of which could not be defined. There was no aqueduct of Sylvius or any direct communication between the third and fourth ventricles. The fourth ventricle was wide, and its floor was covered by thick exudate. The olfactory bulbs were present and small. Considerable thick exudate was present over the optic chiasm. The optic tracts posterior to their decussation became flattened and merged into the pes pedunculi. The geniculate bodies cannot be defined.

The *anatomic diagnosis* was: agenesis of frontal cerebral hemispheres, maldevelopment of the third ventricle, geniculate bodies, optic thalamus, optic tracts, corpus callosum, and fornix, absence of aqueduct of Sylvius, microphthalmus, external hydrocephalus, purulent meningitis, and bronchopneumonia.

Microscopic examinations.—In the brain, sections through the cortex of the frontal lobes showed some proliferation of the glial cells in the superficial layers and invasion with small round cells. There was a marked deficiency and defective growth of the ganglion cells, while in the deeper portion of the entire cerebral tissue there were many vacuolated areas, apparently due to degenerative changes in the neurones. The blood vessels throughout the brain showed no pathologic changes, except a slight hyaline degeneration of their walls. Levaditi's stains did not reveal the presence of spirochetes. The leptomeninges throughout the cortex, midbrain, and pons were invaded by an acute suppurative process. The ependymal lining of the lateral ventricles was destroyed and the subependymal tissue invaded with round cells and polynuclears, which in areas formed cuffs about the blood vessels. The third ventricle was small and patent, its lumen partially filled with albuminous material; the lining ependymal cells were intact. The quadrigeminal bodies appeared to have an increase in the glial tissue.

The venous sinusoids of the spleen were dilated with red cells, the pulp reticulum containing an increased number of monocytes. The remaining organs showed no remarkable changes.

The microscopic diagnosis was: agenesis of cerebral hemispheres, malformation of brain, acute suppurative meningoencephalitis, and septic spleen.

COMMENT

In the literature there is an accumulation of evidence over the past seventeen years, since Aschenheim[12] reported the first case, that irradiation of a pregnant woman is fraught with danger to the fetus. Either abortion results, or in over 50 per cent of the live births there will be gross defects of the central nervous system and eyes.

The fact that many normal children are born after irradiation of the mother may be explained at least in part by physical factors. The fetus may be protected by the thickness of the mother's abdominal wall, the amount of amniotic fluid, or the position of the fetus in relation to the placenta and source of radiation. The high percentage of lesions of the central nervous system and eyes and the astonishing relative absence of other anatomic defects makes one think that the sensitivity of fetal nervous tissue to roentgen ray and radium is most important. The eyeballs of the early fetus are relatively larger and less protected than later. The chance of injury is proportional to the size of the dose and nearness of treatment to conception and probably to other factors, as intercurrent infections and individual variations in radiosensitivity. On the other hand, some infants are not harmed if the dose of radiation is small and if they are exposed later in pregnancy. It is a generally recognized fact that early fetal nervous and optic tissues are very susceptible to radiation. There is also evidence that irradiation of the mother in places remote from the uterus may also be harmful to the fetus.

The case reported bears out the generally accepted opinion at the present on the harmful effects of irradiation on the fetus. The very

rudimentary brain in a skull of normal dimensions suggests that the fetal nervous tissue was injured but the bones were unaffected. The microphthalmia and small brain in this case are in accord with the association so well shown by Goldstein in human offspring and by many experimenters in animals.

It seems reasonable to believe that after more cases have been reported, certain lesions, particularly in the eyes, will be found pathognomonic of irradiation of the fetus. Microphthalmia is so rare in the general population and in ordinary cases of microcephalus, that its common occurrence in radiogenic microcephaly suggests that it represents a specific lesion of radiation.

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1160 PARK AVENUE

OXYGEN THERAPY BY THE OPEN BOX METHOD

DANIEL J. PACHMAN, M.D.
CHICAGO, ILL.

THE open box method of administering oxygen was first described a few years ago by Burgess.[1] When oxygen was allowed to flow at a steady rate into the bottom of an open top box whose sides and floor were impermeable to air, it was found that oxygen concentrations as high as 60 per cent could be obtained within the box. Since the publication of the first description of this method, various changes in the original apparatus have been made.[2, 3]

At the present time, the type of apparatus described below is being used at this hospital to administer oxygen to young children and infants (Figs. 1, 2, 3).

The sides and back are made of a light nonporous wood. Cleaned, noninflammable x-ray films are used as transparent windows in the sides. Rubberized cloth forms the bottom of the box, but in front is replaced by a transparent rubber material, Pliofilm.* The removable bottom and front is made in one piece and is fastened in place by strips of wood and thumb screws. In this manner the entire bottom is made airtight. In the lower front is placed the aperture for admitting the head of an older child, or the head, thorax, and arms of a small infant. A nine-inch zipper allows this opening to be made larger.

In the rear of the apparatus is the ice compartment which aids in maintaining a comfortable temperature and humidity within the box. Rubberized cloth acts as a baffle plate, separating the ice compartment from the front portion. A metal ice container which has a tube in its base is suspended from a cross bar and is filled with ice about the size of refrigerator cubes. Melted ice is drained from the tube of the container through the sides of the box by means of rubber tubing into a collecting pail on the floor. The container also has a false bottom, and within it is a sponge to absorb condensed moisture. A hinged board acts as a cover to the ice cooler compartment. The oxygen inflow from a tank and regulator enters the side of the box directly on one side and the outlet for the drain is on the other.*

The oxygen content within the box can be determined fairly accurately by means of a simple oxygen analyzer. This apparatus is a modification of the method described by Henderson and Greenberg and measures the sum of oxygen and carbon dioxide.[4] However, the carbon

*Pliofilm is manufactured by the Goodyear Rubber Company, Akron, Ohio. Double thickness No. 250 is used.

From the Department of Pediatrics, University of Chicago.

Presented in part at the meeting of Region III of the American Academy of Pediatrics, Chicago, Oct. 15, 1937.

dioxide content of the bottom of the box has been found to be below 2 per cent and is therefore of little practical significance.

Three inches of the lower end of a six-inch tube are blown so that the end will contain approximately 20 c.c. of air.* Steel wool is then lightly

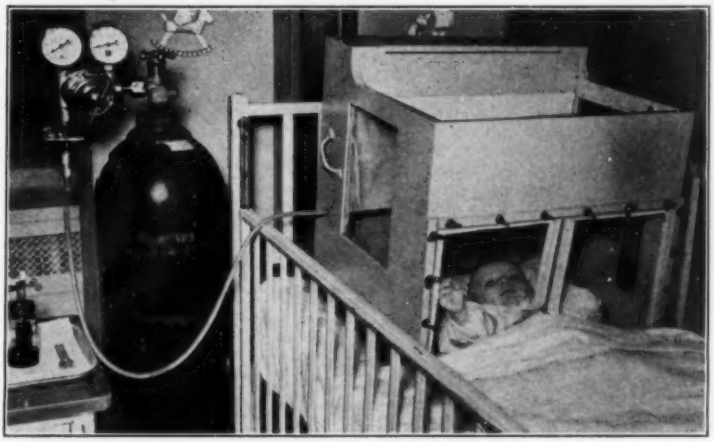

Fig. 1.—View of box in use showing a 4-month-old infant within it. The oxygen analyzer is seen at the left.

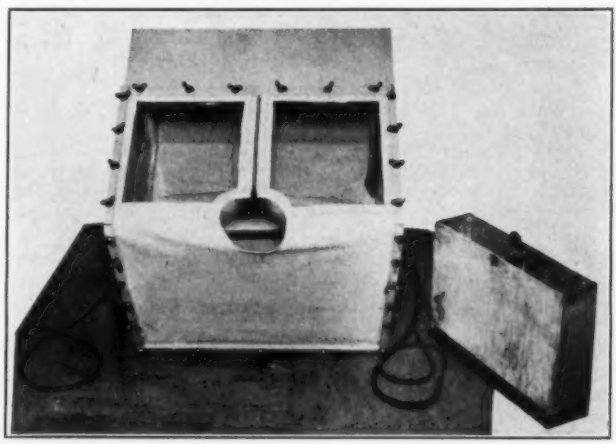

Fig. 2.—View of box showing the floor and the front piece. The ice cooler is pictured at the right.

packed into the wide end of the tube. The narrow end of the tube is pushed through a two-hole rubber stopper. The apparatus is inserted into a wide mouthed glass bottle (180 c.c.). The bottom of the wide

*Gooch crucible holders (25 mm. width), obtainable from E. H. Sargent Co., Chicago, Ill., may be used instead.

end of the tube rests about one-fourth inch from the bottom of the bottle. A rubber tube (one and one-half inches) is then attached to the glass tube protruding through the rubber stopper, and a pinch clamp is

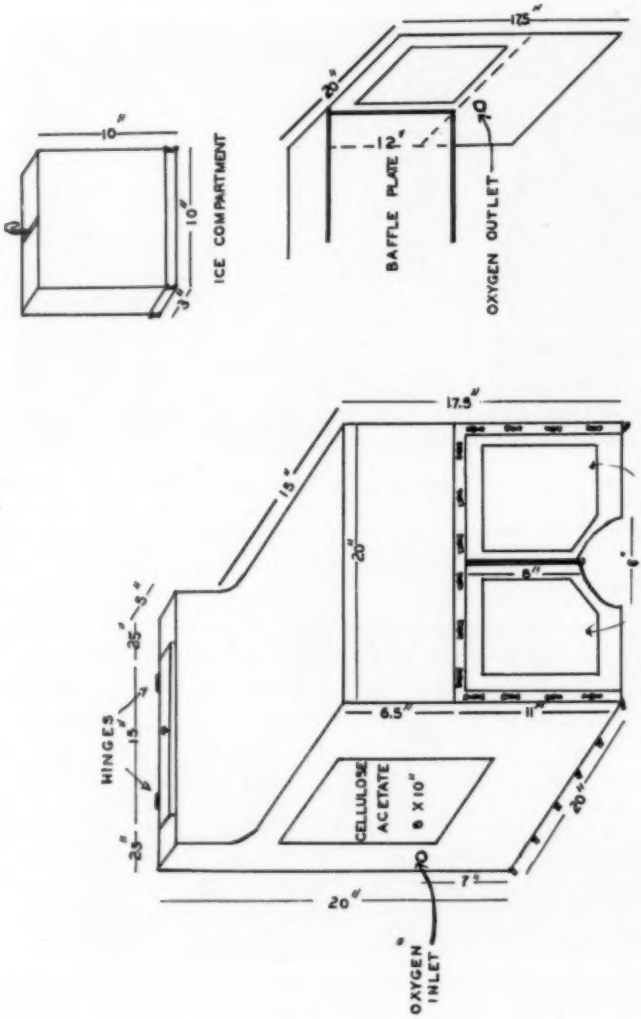

Fig. 3.—Dimensions of the various parts of the apparatus.

placed on the tubing. Feiser's solution, made in the following manner, is then placed in the analyzer bottle:

(a) Sodium hydrosulfite, powder, 40 gm. (technical).
Sodium anthroquinone beta-sulfonate 5 gm.

These are mixed together and 11 gm. are placed in each of four well-stoppered bottles.

(b) Sodium hydroxide (6 per cent solution) 60 c.c.

When ready for use, contents of one small bottle containing mixture described in (a) is mixed with this sodium hydroxide solution (b).

A 10 c.c. syringe is then attached to the open end of the rubber tubing, the clamp released, and fluid drawn up to a marker on the glass tube. The clamp is then replaced, and the analyzer is ready for use.

Procedure.—After releasing the clamp, 10 c.c. of atmospheric air (oxygen concentration 18 to 20 per cent) is placed by syringe into the analyzing solution through the rubber tube. The clamp is then replaced. The level of the fluid in the glass tubing will be changed and after three to four minutes, the syringe is attached, the clamp released, and suction applied until the initial level is reached. The oxygen content is then read from the syringe. For example, if the plunger is at 8 c.c., then 2 c.c. has been absorbed (oxygen) and there is an oxygen concentration of 2/10 or 20 per cent in the air. The air within the box is then tested. A 10 c.c. sample is obtained at the level of the patient's nose, and the procedure outlined previously is carried out.

CHART I

Name: R. H. Unit No.: 183421
Division: BR-3 Clinic or Service: Pediatric

DATE	TIME	OXYGEN CONCENTRATION IN AIR	OXYGEN CONCENTRATION IN TENT	LITERS PER MINUTE ON GAUGE	TEMP. WITHIN BOX	ROOM TEMP.	REMARKS
6-13-38	Oxygen Started 2:15 P.M.			6			
6-13-38	2:30 P.M.	20%	48%	6	76	78	Reduced to 5 liters.
6-13-38	3:30 P.M.	20%	60%	5	76	78	Rm. humidity 36; box humidity 42. Oxygen reduced to 4½ liters.
6-13-38	7:30 P.M.	20%	48%	4½	78	78	Oxygen reduced to 3½ liters.
6-13-38	11:30 P.M.	22%	62%	3½	76	76	Rm. humidity 40; box humidity 40.
6-14-38	3:30 A.M.	22%	64%	3½	78	76	Rm. humidity 42; box humidity 41.
6-14-38	7:30 A.M.	20%	43%	4	76	76	Left at 4 liters.
6-14-38	11:30 A.M.	20%	43%	4	74	74	Left at 4 liters.
6-14-38	3:30 A.M.	20%	50%	4	74	74	Patient coughing a good deal.
6-14-38	7:30 P.M.	20%	50%	4	74	74	Oxygen reduced to 3½ liters. Patient comfortable.
6-14-38	11:30 P.M.	20%	48%	3½	74	74	Rm. humidity 48; box humidity 48. Oxygen increased to 4 liters.
6-15-38	3:30 A.M.	20%	60%	4	74	74	Oxygen reduced to 3½ liters. Child comfortable.
6-15-38	7:30 A.M.	20%	58%	3½	74	74	Left at 3½ liters.
6-15-38	11:30 A.M.	20%	50%	3½	76	76	Oxygen increased to 4 liters.
6-15-38	3:30 P.M.	20%	50%	4	76	76	Left at 4 liters.
6-15-38	7:30 P.M.	20%	48%	4	80	80	Child comfortable.
6-15-38	11:30 P.M.	20%	40%	4	78	78	Oxygen increased to 4½ liters.
6-16-38	3:30 A.M.	20%	48%	4½	76	76	

Humidity recorded as relative humidity.

The air within the box is analyzed every four hours and is recorded on a special oxygen therapy chart (Chart 1). The oxygen content of atmospheric air is constant (18 to 20 per cent) and can be used as a check on the accuracy of the analyzer.* The liters of oxygen used per minute are read off from the gauge. The remarks column is used for any notes such as, oxygen inflow increased, child cyanotic, humidity within the box, etc.

Using the open top method, with an inflow of 4 to 5 liters of oxygen per minute, oxygen concentrations as high as 64 per cent have been obtained at the level of the patient's nose.

A cover is necessary for the ice water compartment as it is believed that convection currents, attracted by the cold, would otherwise force oxygen-rich air upwards from the bottom. The presence of leaks in the floor of the box, or in the lower portion, have a decided effect upon the concentration of oxygen. Oxygen-rich air may escape from around the collar and lower the oxygen concentration. Cotton gauze or batting around the child's neck or chest may be used to prevent leakage. Drafts of air in the room may interfere with the proper operation of the apparatus, and can be prevented by placing a metal screen between the box and the open window.

The explanation of the mechanism of this method of oxygen therapy has been given as follows: (1) There is a balance between inflow of oxygen and its diffusion upward; (2) oxygen is slightly heavier than air; and (3) when cooled tends to sink to the bottom. Removal of the ice cooler, however, has little effect on the oxygen concentration. The end result may be due to a combination of (1) and (2).

The advantages of this type of apparatus are many:

1. It is very inexpensive to make and to operate.
2. It is very simple to operate as no motors are needed.
3. The apparatus is portable and can be used in the home.
4. Children can be fed without removal from the box.
5. The pliofilm windows allow for clear vision from within as well as from without. The children are not apprehensive.
6. Examinations and treatments can be carried out without removal of the patient from the box.

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*New solutions are necessary about every three to four days or when a white film appears.

Critical Review

IMMUNITY AND SUSCEPTIBILITY TO DISEASE IN EARLY INFANCY

CHARLES F. MCKHANN, M.D., AND ISRAEL KAPNICK, M.D.
BOSTON, MASS.

THE distribution and severity of disease in early infancy would appear to be affected by climate, local environment, race, and family as well as by the nutrition and the individual physical characteristics of the infant, all acting more or less through the immune responses of the patient to the frequency and closeness of contact with the disease. Infrequency of exposure may affect the incidence of disease in the newborn infant, yet it fails to account for the remarkable resistance to certain diseases and fails to prevent a sizable incidence of other diseases within a few weeks of birth. Thus not the least important factor is the immunologic make-up of the infant.

Clinical observations have established that the newborn infant is immune to certain disease processes and susceptible to others. Furthermore, it is evident that infants develop resistance to disease poorly and that the characteristic manifestations of some disorders are greatly influenced by this lack of immunologic response. Also we may derive from the immunologic response indications as to the optimal time to begin active immunizations.

The newborn infant is immune up to several months of age to measles, scarlet fever, poliomyelitis, and diphtheria, but is susceptible to pyogenic infections, colon bacillus infections, and to pertussis; a transient immunity of a few weeks may be observed to chicken pox, vaccinia, and to pneumococcus and influenza bacillus infections. Allergic manifestations appear rarely before the fourth month; hemorrhagic nephritis is observed uncommonly under 18 months of age; and rheumatic fever is seldom encountered in children under 2 years of age. It is further well known that arthritis of rheumatic type or atrophic character or even proliferative type is almost never encountered in infancy whereas suppurative involvements of the joint are seen comparatively frequently.

Certain diseases such as typhus and undulant fever occur in infants less commonly and in less severe form than in adults. Although the incidence of yellow fever has been noted to be greater in children than in adults, the course is usually mild.

Infants under a few months seem definitely resistant to the common cold. Pneumonia is uncommon in the early weeks of life but thereafter rises rapidly in incidence. Pneumonia in infants is often not of lobar distribution but is of diffuse infiltrating type. The interstitial pneumonitis so frequently observed may well be due to the inability of the patient to localize the pneumonic process. Staphylococcal infections are virulent in early infancy and frequently cannot be dis-

From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals, Boston.

tinguished from streptococcal infections. Thus cellulitis in the newborn infant may be due to the staphylococcus, and dermatitis exfoliativa and pemphigus neonatorum may represent unopposed staphylococcic skin infections.

The incidence and character of meningitis in infants have been studied by Fothergill and Sweet.[1] Apparently the transient resistance present at birth to the pneumococcus and influenza bacillus is lost within a few weeks and the patient then becomes extremely susceptible to meningeal involvement with these organisms. Colon bacillus meningitis is observed infrequently but because of its age distribution may be considered a disease of the neonatal period. Newborn infants are susceptible to pertussis, which is particularly dangerous at this age. Only infrequency of exposure prevents a sizable death rate of infants from pertussis.

The immunity of the newborn infant is derived from the mother and is mostly passive in character. However, unlike passive immunity following an injection of serum, which immunity lasts only three or four weeks, that observed in the newborn infant lasts in the case of measles for five months, for scarlet fever, six to eight months, and for diphtheria and poliomyelitis equivalent times. Antibacterial immunity is of shorter duration and more nearly simulates artificial passive immunity. After the passive immunity is lost a period of susceptibility ensues greater usually than that shown by older children.

Thus a consideration of resistance to disease in early infancy may be broken down into two phases: (1) the immunity of the newborn infant, transient and passive in character; and (2) the immunologic responses, active in character, which occur in the newborn and young infant.

IMMUNITY IN THE NEWBORN

The basis of the selective immunity to disease that is observed in newborn infants might be due to:

1. Transplacental transmission of (a) antigen from the mother, resulting in active intrauterine immunization of the fetus, and (b) antibodies from the mother, producing passive intrauterine immunization.
2. Transmission of antibodies from the mother to the infant through colostrum and milk.
3. Tissue immunity of the rapidly growing infant.

PERMEABILITY OF THE PLACENTA TO BACTERIA AND VIRUSES

Many observations have been made on the permeability of the placenta to bacteria and to viruses. A secondary question has been whether the placenta is normally permeable to bacteria, or whether lesions must occur locally for transmission to take place. It seems probable that organisms cannot pass through the healthy placenta, but that they can pass after pathologic processes have damaged the organ.

The transmission of syphilis is well established and is unfortunately common. It is possible that the morphology of the *Treponema pallidum* allows it to penetrate the placenta more easily than can other organisms. Congenital malaria must also be considered as proved, judging from reports in the literature.[2]

The leprosy organism reaches the fetus in a considerable number of cases, and intrauterine infection in leprosy must be considered, particularly when the disease develops in early infancy.[3]

Congenital pneumonia has been observed repeatedly and may be a cause of stillbirth.[4] Placental transmission of gonococcic infection apparently can occur, as indicated by the appearance of gonococcic polyarthritis in the newborn infant.[5] One of us has observed two such cases.

Congenital tuberculosis probably occurs in rare instances; however, infection is usually by postnatal contact and if the infant of a tuberculous mother is removed from the infective surroundings immediately after birth, tuberculosis usually does not develop.

The filterable viruses readily penetrate the placenta. Infants have been born showing definite signs of measles, chicken pox, and smallpox, evidences of intrauterine infection with these diseases. The authors have observed instances of chicken pox and smallpox in the newborn infant. There are several reports in the literature of intrauterine poliomyelitis. However, a case observed by the authors as well as consideration of the distribution of the poliomyelitis virus in the body indicates that such transmission probably does not occur. In our case a mother who had had poliomyelitis when five months pregnant was delivered of an infant who showed no evidence of the disease and who was only passively immune to it. The failure of the virus to enter the blood stream would account for this lack of similarity to other virus diseases. The transmissibility of rabies virus has been demonstrated in dogs and rabbits,[6] and Herrmann[7] has confirmed the passage in man by inoculating animals with brain emulsion of fetuses from pregnant women that had died of rabies infection. However, the virus in the brain of the fetus was decreased in virulence.

Experimental studies have been made on changes in placental permeability due to damage by various agents. Ueda[8] found that the toxins produced by the typhoid and dysentery bacilli, streptococcus, pneumococcus, and staphylococcus contracted the blood vessels of fresh mature human placentas. Ueda suggested that the interruption of pregnancy frequently seen in acute infectious diseases may be due to the action of bacterial toxins on the placenta.

PLACENTAL TRANSMISSION OF ANTIBODIES

An extensive literature exists on the transmission of antibodies through the placenta. The human placenta is permeable in variable degree to antitoxins, precipitins, bacteriolysins, complement-fixing antibodies, and to some of the natural antibodies. All of these yield a purely passive immunity which disappears within periods of time varying somewhat with the specific antibody.

The placental transmission of diphtheria antitoxin in the human has been studied repeatedly.[9] The passage of tetanus antitoxin has also been established.[10] In most cases the blood of the infant at birth contains the same concentration of diphtheria antitoxin as the mother's blood, but gross divergences have been noted. Kuttner and Ratner[11] made accurate quantitative determinations of diphtheria antitoxin in infant's, mother's, and cord blood by the Kellogg method, and found no loss of antitoxin by passage through the placenta. The concentration of antitoxin in the cord blood corresponded to that in the blood of the mothers.

The antitoxic substance to scarlet fever is also present in the umbilical cord blood. The blanching of scarlet fever rashes with placental serum was found by Toomey[12] with 79 per cent of 227 serums.

Some serums blanched the scarlet fever rashes as well as did convalescent scarlet fever serum. The ability to neutralize Dick toxin in vitro was demonstrated in these same bloods. The conclusion that the immunity of the newborn infant to scarlet fever represents in large part a passive transfer of antitoxin from the mother seemed justified.

The serum of infants contains little opsonin for virulent hemolytic streptococci, and even this small amount is lost in a few weeks.[13] The age distribution of antistreptolysin is similar to that of naturally acquired diphtherial and scarlatinal antitoxin.[14] The infants' titer, equal at birth to that of the mothers', diminished rapidly during the first few weeks of life. Lippard and Wheeler[15] made the interesting observation that antifibrinolytic substance was usually present in the newborn infant in much higher concentration than in the mother. Lippard and Johnson[16] found that children under 3 years of age lacked the capacity to develop resistance to fibrinolysis.

The neutralization of poliomyelitis virus by umbilical cord blood has been adequately demonstrated.[17]

The newborn infant is immune to measles if the mother has experienced the disease. The passive character of the immunity was shown by Herrmann[18] and by Debré and Joannon.[19] Finkelstein,[20] Jorge,[21] and de Souza[22] have reported the use of placental blood serum in dosage of 10 to 60 c.c. in prevention of measles.

Bryce and Burnet[23] also note that apparently the placenta becomes less permeable for maternal antibodies during the later months of pregnancy.

Umbilical cord blood and the blood of newborn infants contains staphylococcus antitoxin in practically the same amounts as the maternal blood.[23] This is lost during early infancy and is followed by a gradual rise in antitoxin during later years to what is assumed to be a normal level. Agglutinins against typhoid were found to pass the placenta by Scholtz,[24] Schumacher,[25] Staubli,[26] Mosse and Daunie,[27] and more recently by Peduzzi.[28] Timmermann[29] found that the H and O agglutinins pass unequally through the placenta. The H form passes in most cases and the O passes seldom if at all. The authors have witnessed two cases of typhoid in pregnant mothers whose infants had negative agglutination reactions in cord blood. A similar case was reported by Neff and Schwartz.[30] An infant was born three weeks prematurely of a mother in the third week of typhoid fever. The mother's Widal reaction was positive in 1:2560. The infant's cord blood was negative; culture of cord blood was also negative. One month after birth the infant's Widal was positive in 1:20,480, the highest dilution ever observed in that laboratory. The infant was formula-fed and had had no contact with the mother after delivery. This case suggests that the antigen rather than the antibody passed the placenta and that the infant within a few weeks developed antibodies of his own. Cooke[31] has shown the complement-fixing antibody of tuberculosis to be transferred from mother to offspring. Halban and Landsteiner[32] found maternal bacteriolysins in the infant's serum but in a lesser concentration than in the mother's. The isoagglutinins in the newborn infant are not developed by the fetus but are derived from the mother and transmitted through the placenta, and agree closely with the level found in the mother's serum.[33] The isoagglutinins present at birth disappear within ten days to two or three

weeks and are gradually replaced by the child's own, which then remain throughout life. Occasionally isoagglutinins may be present in the newborn which were lacking in the maternal blood so that they must be derived from the infant's organism.[34] Probably there is a transmission of this natural antibody through the placenta, and the fetus can also elaborate isoagglutinins of its own, providing they are compatible with the mother's blood. Nattan-Larrier[35] found that fetal blood does not contain natural antisheep hemolysin, although it can be demonstrated simultaneously in mother's blood. Artificially produced hemolysin, on the other hand, passes through the placenta. He found also[36] that pseudoglobulin was the principal if not the only carrier of the antitrypanosomic substance of the human serum, while euglobin was the carrier of the antisheep hemolysins of human blood. Both the antitrypanosomic and hemolytic substances were incapable of traversing the placenta. Nattan-Larrier took this as evidence of the nonidentity of natural and artificial hemolysin. Nattan-Larrier and Richard[37] found that maternal alexin did not pass the placenta. Von Oettingen and Witebsky[38] have presented evidence to show that the tissues of the placenta show no group characteristics. The placenta acts apparently as a neutral organ between mother and fetus and hence in heterospecific pregnancies the fetus cannot be injured by the mother tissues.

The possibility of both active and passive sensitization in utero brings up the question of the transmission of proteins through the placenta.

Infants may be born of nonsensitive mothers and yet manifest profound anaphylactic symptoms when they ingest some protein food for the first time.

Ratner[39] presents clinical evidence for the possibility of active sensitization in utero in cases where the mother had overindulged in certain protein foods, such as nuts, eggs, and wheat, during her antepartum period. After birth the infant, with a predisposition for allergy, manifested some form of allergic phenomenon when coming in contact with this food for the first time. The antigenic proteins enter the maternal circulation in an unchanged state from the intestinal tract and thereby gain entrance to the fetal circulation.[40]

Cooke and Vander Veer,[41] Spain and Cooke,[42] and Clarke, Donnally, and Coca[43] have shown that there is a tendency for the children of asthmatic parents to develop asthma and for those of parents suffering from hay fever to develop hay fever. This led Bell and Eriksson[44] to study the transfer of skin-sensitizing antibodies from mother to offspring in cases of asthma and of hay fever. Direct testing and the Prausnitz-Küstner method of passive transfer were used. Mother's sera reacted positively in all cases, and cord and infant's blood, negatively. Presumably skin-sensitizing antibodies were not transferred through the placenta.

From the available evidence it may be concluded that active and passive sensitization in utero can occur.[45]

TRANSMISSION THROUGH COLOSTRUM AND MILK

The role of colostrum in the transmission of antibodies in animals was noted by Famulener[46] and was emphasized by the work of Smith and his collaborators[47] who found that colostrum was essential to the newborn calf in the prevention of colon bacillus septicemia. Howe[48]

demonstrated that the serum of the calf was deficient at birth in both pseudoglobulin and euglobulin and that after the ingestion of colostrum these globulins, the antibody carrying proteins of the blood, rose rapidly to normal levels. Lewis and Wells[49] and Boyd[50] showed that the human placenta allows the passage of pseudoglobulin in undiminished quantity, and only euglobulin is held back. Kuttner and Ratner[11] found that transitional milk and later milk did not contain antitoxin. Human colostrum occasionally contained small amounts of antitoxin, but the antitoxin content of infant's blood showed no increase attributable to colostrum feeding. Ratner, Jackson, and Gruehl[51] reviewed the evidence and concluded that colostrum was essential for the transmission of immunity in goats and cattle, but that it played a negligible role in man. There is also inadequate evidence for the passage of sensitizing proteins through the human colostrum or milk.[52] The transmission of antibodies through the later milk was also studied without evidence for this mode of transmission in humans.[52] However, Toomey[53] has recently studied the agglutinins against the enteric group of organisms in mother's blood, baby's blood, mother's milk, and placental blood. The agglutinins were transmitted through the placenta, but the amount was small and much less than the titer shown by the mother's serum which usually contained massive agglutinins against the enteric group. The blood serum of the infant, 10 days after birth, showed a marked increase in agglutinin titer over the placental serum. Since the titer of the infant's serum approximately paralleled that of the mother's milk, it seemed probable that the milk was the source of the agglutinins.

TISSUE IMMUNITY

Instances are recorded of infants who were immune to scarlet fever and to diphtheria whose mothers were demonstrated to be susceptible to these diseases. Placental or mammary transmission of immunity does not explain these phenomena; so a third possibility has been suggested, designated "tissue immunity" of the young.[54] The ability of embryonic tissue to neutralize diphtheria toxin as well as the resistance of embryonic tissue to tumorous growths is pointed to as evidence of this.[55]

PRACTICAL APPLICATION

Two practical applications have been made of the transplacental transmission of antibodies.

Nattan-Larrier, Ramon, and Grasset[56] have shown that it is possible to protect the newborn infant against tetanus by injecting the mother with tetanus toxoid before the birth of the infant; the protection derived from his procedure lasts for about two months, suggesting that the antibody developed by the mother rather than the injected toxoid traverses the placenta. This method of rendering infants temporarily immune has been used in Africa and in China, where childbirth tetanus is very common.

Placental extracts have been made and used effectively in the prevention and modification of measles.[57] In addition to measles antibody these extracts contain diphtheria antitoxin, scarlet fever antitoxin, antistreptolysin, and antibodies neutralizing poliomyelitis virus. Variable amounts of antibacterial substances are also demonstrable. An effect of placental extract on the inhibition of vaccinia in chick embryo cultures has recently been demonstrated. An interesting observation resulting

from the studies of placental extract has been that the antibodies occur not only in the blood serum of the placenta but throughout the tissues of the organ. This storage of antibodies in the tissue may reflect a similar condition in the infant and might account for the long passive immunity in infants to certain diseases.

DEVELOPMENT OF IMMUNITY IN INFANTS

The respiratory and gastrointestinal tracts of newborn infants are sterile[58] but soon become the habitat of a variety of organisms. Kneeland[59] followed the bacteriology of the nose and throat in infants throughout the first year of life and found that the respiratory tract, sterile at birth, soon reflected the flora of normal adults. Pathogens were usually absent till the infant was 2 or 3 months of age, suggesting that type of contact may play a role in the bacterial seeding process. The first colds of infants were mild and were accompanied by no alterations in normal bacteriology. Barenberg, Greene, and Abramson[60] reported that institutional children were more susceptible to pneumonia between the ages of 6 months and 2 years, and that the case rate below 6 months was very low. Kneeland and Dawes[61] followed a similar group of infants and also found that infants in the first few months were comparatively immune. After 18 months children had many colds but were moderately resistant to pneumonia. Infants from 8 to 14 months had fewer colds but were highly susceptible to serious respiratory disease, especially pneumonia. Sutliff and Finland,[62] working along the same lines, found that bactericidal power against the pneumococcus was present in many infants in the first ten days of life but from two months was absent or very rare. From two to eleven years pneumococcidal power again returned. The bactericidal power of infants' blood was less in degree but reflected qualitatively the mothers' bactericidins. Negative skin tests to protein and to autolysate in the newborn infant indicated that reactivity to specific antigens was not passively transferred from the mother.

Fothergill and Wright,[63] studying influenza meningitis, pointed out the relation of the age incidence to the bactericidal power of the blood against the causative organism. These authors found that *influenza* meningitis is rarely seen under 2 months of age or beyond 6 years. Eighty per cent of reported cases have occurred between ages of 2 months and 3 years. Cord blood and blood of infants under 2 months had considerable bactericidal power while that of infants between 2 months and 3 years had practically none. After 5 years the bactericidal power gradually rose to adult levels. Davies[64] tested the response of infants to inoculation with Type I pneumococcus carbohydrate and found the reaction much less than that observed in older children and adults.

These results are in agreement with a considerable amount of evidence which indicates that the development of immunity in infants differs from that in older children and in adults.[65] The development of natural antibodies such as isoagglutinins may be taken as indicative of the ability of the infant to develop immune bodies. The patient's own isoagglutinins are seldom apparent under one month and do not usually reach their adult titer until 2 years.[66] Natural hemolysins to heterologous red cells are absent from the blood of newborn infants, even though present in the mother. They develop gradually in the infant, reaching about 20 per cent of the adult level by the end of the first year of life.[67]

The same general tendency for the development of antibodies with advance of age is seen in the case of diphtheria antitoxin.[68] Very young children not only develop diphtheria antitoxin slowly from spontaneous contact with the organism, but they respond in less degree to the injection of toxoid or of toxin-antitoxin mixtures than do older children.[69] At the end of the second year of life, when the great majority of children have developed their particular blood group, the proportion whose serum contains protective amounts of diphtheria antitoxin is almost at its minimum. That lack of contact with the antigen is probably of influence in the slow development of immunity to diphtheria is indicated by observation of persons isolated from large groups who develop immunity only in adult life. The results of large numbers of Dick tests indicate a definite relation of age to the development of immunity to scarlet fever even slower in its appearance than that to diphtheria.[70] The situation with respect to poliomyelitis would seem also analogous to that of diphtheria, although the data on immunity to this disease are not extensive.[71]

Freund[72] has been interested in the problem of age and immunity, and has studied the subject experimentally finding that the formation of agglutinins against typhoid bacilli, of hemolysins against sheep cells, and of precipitins against horse serum and egg white was less intense in young animals than in adult animals immunized in the same way. Frankenstein[73] found in infants that only an occasional subject produced agglutinins after inoculation with typhoid vaccine. Other workers have found that the response to typhoid vaccine occurs but is definitely less marked than in older children.[74]

Age is also of significance in the development of skin reactivity as has been noted in the slow development of a positive tuberculin reaction in young infants[75] and in a tendency to be nonreactive to Dick and Schick tests even in the absence of the specific antibody from the blood stream.[76] Reactions to skin tests with pneumococcic antigens were also minimal in infants[77] as were those to intradermal injections of colon, typhoid, streptococcus, and other bacterial extracts.[78]

The factors which influence the rapidity and extent of development of natural and artificially stimulated antibody response in infants are little known, and considering the importance of this subject in the field of pediatrics the attention devoted to it has been inadequate. Nutritional habits, types of food, character of environment, the endocrine make-up of the patient, family or racial differences may be among the forces operative.[79]

Racial resistance, examples of which are numerous, will be reflected in the individual, yet the infant often shows least of the evidences of the racial immunity. The importance of diet is exemplified in the infected corneal or pulmonary lesions in Vitamin A deficiency and has been further defined in experimental studies of the relation of diet to infection.[80] An endocrine maturation phenomenon may be indicated by the experiments of Jungeblut who rendered normal young monkeys insusceptible to poliomyelitis through repeated injections of pituitary extracts.[81] The influence of one disease in predisposing to another by increasing the individual susceptibility is too well known in pediatrics to require more than mention. Certain types of infants seem to be even more susceptible than the group as a whole. Thus in an epidemiologic survey[82] of infections arising in a group of hospitalized infants only 5.5 per cent of previously well infants be-

came infected, whereas 19 per cent of premature infants, 35 per cent of chronically malnourished and 17 per cent of luetic, eczematous, and congenitally defective infants were involved. Scorbutic infants were highly susceptible to infection while rachitic infants were no more so than normal infants. Little is known of the immune responses of premature infants and whether debilitated patients and those suffering from deficiency diseases develop the ability to produce antibodies at times chronologically comparable to normal infants. Here is a large field awaiting exploration. It is hardly more than necessary to indicate the general influences of overcrowding, poverty, and other social and environmental factors.

Hirszfeld[83] has introduced the concept of serologic maturity which does not deny the influence of antigenic stimulation but assumes that the age or constitutional nature of the individual must be of the state to permit the immunologic response. Grasset[84] with a similar concept speaks of a curve of aptitude to acquire immunity. It is interesting to note that a disability to produce immune bodies similar to that in infants occurs in aged persons

We may tentatively conclude that immunity in the young differs from immunity of later ages (except possibly advanced age) through the interaction of two factors: (1) the specific antigen; (2) a state of immunizability, reflecting the capacity of the infant to respond to contact with the antigen. The failure of a response to contact with the antigen may result from its neutralization by the passively acquired antibody derived from the mother or may be traceable to the absence in the infant of the development permitting antibody production. Until immunologic maturation has taken place natural antibodies do not appear, and attempts at artificial immunization may have little result. If the antigenic stimulus is great, antibodies may be formed even during this early period, but they seldom reach any magnitude and tend to sink rapidly to low levels. The time of appearance and the strength of the reaction vary somewhat with the individual. Most infants respond slowly to antigenic stimulation yet a rare patient will have a rapid or efficient response, even in earliest infancy.

The necessity of contact with the antigen is shown by the tendency of antibody titers to fall unless antigenic stimulus is repeated at intervals. In infants, however, the factor of immunizability deserves more careful study. One should not be satisfied with the term serologic immaturity but must attempt to establish by chemical and physiologic studies the basis of such immaturity. Is the genesis of plasma proteins the important factor? Do dietary deficiencies or endocrine development play roles? As yet these are questions that cannot be fully answered but which should be objectives of persistent research.

Although the basis of the immunologic response of infants is poorly defined, a survey of the situation may serve to guide certain parts of daily practice.

The newborn infant is immune to many diseases by reason of passive transfer of antibodies from the mother. After the passive immunity is lost the infant becomes susceptible—more susceptible than the older child. This susceptibility appears to depend on a deficiency in the ability to produce antibodies. The deficiency is associated with a similar low level of natural antibodies such as isoagglutinins and heterophile antibodies.

From this we may derive that a lessened response to active immunization must be expected in infants and that a further diminution in response occurs if immunization is attempted before the natural immunity is lost. Thus a toxoid immunization against diphtheria will secure a larger percentage of solid immunizations if it is done after the passive immunity derived from the mother is gone and further if it is done late in infancy, when immunizability is rising. The young child responds even better than the infant, but undue delay must be weighed against the possible dangers of exposure in the older patient. Thus immunization against diphtheria, scarlet fever, and smallpox may all be delayed until late in the first year of life without material increase in danger to the infant and with a much greater immune response than would be obtained from earlier inoculation.

In view of the susceptibility of the infant to certain diseases and the character and severity of the disease process at early ages, therapeutic measures available for adults should be extended to infancy. We are now in such a transition in the treatment of pneumococcus pneumonia. A few years ago serum was employed in the treatment only of lobar pneumonia. Now serum treatment has extended to treatment of all pneumococcus pneumonias, and as serum becomes available for the types found in infants, serum therapy has been extended with very gratifying results into this age group.

SUMMARY

The immunity of the newborn infant to certain diseases is passive in character and is soon replaced by susceptibility more marked than that of older individuals. This great susceptibility may account for many of the unusual characteristics of disease in infancy and is dependent apparently on a deficiency in the capacity of the infant to produce antibodies.

This deficiency requires that more intensive therapy be applied toward infectious disease in infancy wherever such therapy is available, e.g., as in serum treatment of pneumonia.

Also the inadequate antibody response in early infancy should lead to delay in the active immunizations at least until the second half year of life when passive immunity derived from the mother has been lost and immunizability of the infant is rising.

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American Academy of Pediatrics

Proceedings

EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DEL MONTE, CALIF., JUNE 9, 10, AND 11, 1938

Round Table Discussion of Clinical Immunology

Chairman: Dr. K. F. Meyer, San Francisco, Calif.

Some Fundamental Principles in Clinical Immunology

K. F. Meyer, Ph.D., M.D.*

The classical methods of controlling a communicable disease consist of procedures which prevent the transmission of the infective agent. This so-called exposition prophylaxis is directed against the existence and distribution of the disease agent and is primarily applicable to the diseases which are colloquially designated as avoidable. Sanitation of the environment, with special reference to the protection of the food and water supplies, effectively suppresses, in fact, eliminates these diseases.

In principle, these general measures are mostly ineffective in the control of the so-called civilization diseases, since contagion is eventually a function of the crowding and intimate contact of human beings, and thus unavoidable. Without a thorough knowledge of the epidemiology of the disease, it is obviously impossible to institute prophylactic measures based on isolation, disinfection, and control of carriers. Isolation as a means of suppressing measles may be effective provided the importance of notification is more universally appreciated. Physicians are lax in reporting when they know that no service is being rendered by the health department or the community.

The control of diphtheria, scarlet fever and poliomyelitis through isolation is extremely difficult since a relatively small percentage of human beings exhibit signs of the infection in form of clinical disease. In whooping cough the isolation is usually too late. The various procedures of disinfection, except concurrent disinfection, are mostly symbolic and ineffective. A search for carriers from the standpoint of a general control of civilization diseases appeared justified at a time when the so-called practical ubiquity of the disease agents was not known. Today one must be grateful for the failure to eradicate the carriers even if such a procedure would have been temporarily successful. The process of immunization by means of subclinical infections would have been strangulated, and on reintroduction of the disease, the population would have had to meet it in an utterly unprotected state. The experiences on the Island of Nauru (1910) with respect to poliomyelitis and, in fact, on the Faroe Islands (1873 to 1875) in connection with measles, offer excellent examples of what might have happened. General hygienic measures are not very promising, particularly since exposure is not preventable; a protection of the host before the onset of an infection is valuable. This so-called disposition prophylaxis is known as the immunobiologic control of a communicable disease.

*Director, Hooper Foundation for Medical Research.

The noteworthy successes which have been recorded encouraged the belief that a great many other maladies not classed with the civilization diseases may be prevented by an immunobiologic approach. It is doubtless profitable to subject the procedures to a critical inquiry. In this connection one is equally tempted to analyze the vast field of clinical serum and vaccine therapy. Thus before a few selected methods and procedures are chosen for general discussion, it may be appropriate to define the position of the immunologist in its relation to the problems involved.

Nobody will deny that in clinical and in public health work, a critical evaluation of a process of immunization is most important. The present state of affairs is in many ways untenable. A definite dogmatism or doctrinism is evident. This attitude is particularly true in those instances in which one group of workers wishes to *promote* an immunization procedure. The same position is taken when it is necessary to protect a method against an attack by others. This dogmatic concept is accompanied by an unmistakable empiricism. Theoretic considerations or experimental facts are ignored; one proceeds and accepts as conclusive only mass tests on man. The consequences of such a tendency are clearly shown in the attempted immunizations against tuberculosis and poliomyelitis.

Quite generally one is guided by the principle that the immunizations must be harmless. As an ideal, one considers a reactionless vaccination, but an immunization without manifest pathologic consequences or an immunization with a latent reaction is better. The primum non nocere predominates and overshadows the efficacy of a method. In principle, this concept is in my opinion not sound for the following simple reason: If a procedure of vaccination produces no reactions and is relatively harmless, it is reasonable to conclude that it is of little value and consequently its facultative or obligatory use is not justified. If, on the other hand, a procedure is satisfactory with respect to intensity and durability of the protection conferred, severe immunisatoric reactions must be accepted as inevitable, always provided that the risk, inherent to any effective immunization, is quantitatively and qualitatively counterbalanced by the dangers which the omission might entail.

In recent years one justifies the experimentations with an immunisatoric procedure because it is harmless, long before the value or lack of value of a certain method has been accepted by the experts as proved. As a result thousands of human beings have been injected with preparations, and no effort has been made to specify the purpose and the reason for the tests. The introduction of a method of immunization as a means to propagandize such a procedure long before the experimental evaluation of the principle has been completed is certainly not within the jurisdiction of a profession or an agency which is entrusted with the health of the people.

The purpose of all immunizations is the protection of a human or animal host: (1) against the manifest symptoms induced by the infectious process, or (2) the modification of the course of the disease, or (3) a reduction in the case fatality rates. All the known immunobiologic procedures are obviously directed towards the pathogenic effects and not against the infection per se. In fact, a great deal can be achieved provided the immunization transforms the manifest infection into a latent or abortive process.

The observations on measles show how a superimposed latent infection may effectively exert an immunisatoric effect.

Convalescent serum administered after exposure confers an immunity for three to four weeks. On the other hand, if children so treated are exposed a few days later to measles, a permanent immunity of many years' duration will result. Doubtless, the latent minimal infection transforms the ephemeral passive into an active immunity. As a rule, present-day methods are more effective in preventing the localization of an infection than in paralyzing the pathogenic manifestations, since

the factors leading to the disease are unknown. Exceptions to this general conclusion are the bacterial intoxications caused by toxicogenic saprophytes, tetanus and botulism, perhaps diphtheria and certain types of dysentery.

Today some doubts have arisen as to the general concept that the test tube toxins are responsible for the total disease picture in diphtheria and, consequently, the active or passive immunization with these toxins as now practiced may not be the proper method to follow. The present-day position in this matter may be stated as follows:

(1) According to the many observations now available, it is admitted that immunity against diphtheria is primarily antitoxic; however, other factors such as bactericidal forces and primary toxin resistance participate in the defense and recovery from the disease.

(2) A human being lacking one or the other of the functions may contract the disease provided he is sufficiently exposed. In case he lacks every one of the defensive forces, he may pass through a severe disease, and should he be unable to produce them sufficiently or for a long period, the chance of repeated infections is a decided possibility.

(3) As a rule, those who possess an antitoxic immunity or other as yet unknown defensive forces never contract the disease. Furthermore, those who may be able to mobilize humoral and cellular defenses in sufficient quantity at the time of contact with the disease organism may remain unaffected.

(4) The majority of people acquire an immunity to diphtheria either by recovery or through subclinical infection. Intensity and duration of this immunity depend on (a) exogenic (antigenic) factors and (b) genotypic factors (variable ability in the individual to produce antitoxin or other defensive forces).

(5) As a rule, a lowered antitoxin content has been demonstrated at the beginning of the disease. The few exceptions (10 per cent) are attributable to the formation of antitoxin during the first few days of the illness.

(6) It is a fact that in mild diphtheria, without serum treatment during the course of the disease and following recovery, inability to demonstrate antitoxin does not preclude the possibility that the antitoxin, which is generated rather slowly, may be recognizable only after a lapse of several months. These examples merely indicate that recovery and resistance of the host to the diphtheria bacillus are not conditioned by the antitoxin alone.

Next of importance are the latent and abortive infections, which may in themselves constitute a process of immunization of the individual, but at the same time become sources of disease. Such immunizations conducted in population groups may protect the person who has been injected with the infective agent, but may injure the unprotected individual in the immediate environment. For example, the morbilloid or mitigated measles induced by serum prophylaxis is infectious, and experiences in institutions have taught that a new generation of measles within an epidemic or a new epidemic may be traced to such cases. The consequences are quite obvious. Many of the methods of immunization now in use fail to reduce the possibilities for the spread of the infection; in consequence, they will never permit a reduction of an immunization program which has been inaugurated in a certain region. What has been initiated on the present living generation must be continued for an indefinite time if it is desired to maintain the protection of the masses at a high peak. That method of immunization, which prevents the localization of a disease-producing agent and thus transforms a probable host into a nonsusceptible one, will not only protect the individual but will ultimately reach the utopian goal, the radical elimination of the infectious epidemic disease. These considerations lead to the pertinent question: What criteria must be used to evaluate a method of immunization?

Observations during the past thirty years have shown that the recovery from *certain* infectious diseases leaves a dependable and permanent protection against a subsequent reinfection of similar etiology; while in others not only no specific immunity is noticeable, but, in fact, a definite increased disposition is recorded. In the first group predominate the diseases caused by viruses; in the latter the bacterial infections. Although this distinction is not absolute, it is obvious that the efforts in the direction to produce an effective protective immunization are much more promising in the field of viruses than in the bacterial diseases. Furthermore, it is generally recognized that an infectious disease process supplies the protection to a malady of identical nature. As to whether a latent infection induces the same condition is by no means established for every disease. Abortive or latent yellow fever, measles, and Rickettsia may with considerable certainty create protection.

The importance of latent infections as factors in the individual resistance to diphtheria, scarlet fever, and other diseases of childhood is by no means clear. The theory of latent epidemization is based on statistic-epidemiologic mass observations. It is not appreciated that one rarely knows the history of specific infections of an individual who, despite innumerable chances of exposure, remains well. The absence or the presence of antitoxin in the blood is not necessarily conclusive proof that the individual has or has not passed through a latent diphtheritic or streptococcic infection. The epidemiologist has always been puzzled by one fact; the latent infections are not sufficiently widely distributed to induce a far-reaching change in the state of immunity of a large population group. What has been definitely established is briefly this: (1) The morbidity from diphtheria or scarlet fever stands in intimate relationship to age. However, no data are available to prove that this relationship is equally prevalent in the epidemic as well as nonendemic areas, and (2) even in the different age groups, the ability to contract the disease is never uniform. During the period of maximum liability, only a relatively small percentage of the exposed individuals contracts diphtheria or scarlet fever. Members of one family give usually all positive or all negative antitoxin findings. And yet diphtheria rarely selects more than one or two persons in a family (Neisser and Heymann). These and other observations make it doubtful that the latent epidemization is the sole dominant factor in creating the resistance.

Although no final explanation regarding the resistance in diphtheria and scarlet fever may be offered at this time, the procedure to immunize by inducing mild infections is theoretically sound and most useful in many infections. On the other hand, *antigen immunization* with killed organisms or their toxins leaves a great deal to be desired. Even if the injections of vaccines confer a certain degree of protection, it must be emphasized that in such diseases as typhoid, cholera, and plague in which the reports are mostly indefinite impressions and not scientifically proved facts, the duration of the protection, whether for one year or only a few months, is by no means known or definitely established.

Preliminary to any practical application of procedure of immunization, it is important to test its supposed efficacy by animal experiments which are so planned that they give complete information and prevent the physician from disappointments. In this respect, a great deal is still left to chance. The animal stock must be uniform in susceptibility. Quantitative studies must be made on large series; this is particularly true for the evaluation of the toxoids. The question has been by no means settled concerning the relationship of immunisatoric value of toxoid and its flocculating value.

Studies by Prigge in the Ehrlich Institut have shown that toxoids with an equal flocculating value possess variable antigenic properties. Thus it is imperative that the immunizing value of a toxoid preparation be compared by direct tests on guinea pigs of uniform susceptibility. The German regulations proceed in practice as follows: 125 guinea pigs are injected with standard toxoid; an equal

number of animals receives an equal amount of the unknown preparation. Twenty-eight days later each animal receives an injection of test toxin. A preparation which fails to protect the same or a larger percentage of guinea pigs injected with the standard toxoid is refused general distribution. Until toxins standardized according to a like procedure are available, it is doubtless futile to argue the advantages and disadvantages of plain versus alum toxoid. Suffice it to state that alum toxoid is now produced both in Germany and Denmark with an immunizing value of not less than 30 units per 1 c.c. The average plain toxoid contains approximately 1 unit. The use of these highly potent antigens has many advantages but does not preclude the necessity of adhering as heretofore to the fractionated method of immunization.

Despite the noteworthy achievements which the animal experiments have granted the immunologist, it must be frankly admitted that the study is incomplete in many ways. It is impossible to reproduce the infectious disease with respect to portal of entry and dosage of disease agents.

When a method of immunization is ultimately tested on human beings, it is important to divide it into two acts; (1) the immunization and (2) the determination of the refractory state. The latter may be evaluated as follows: (1) by intentional infection, (2) by intentional exposure to a natural infection, (3) by permitting the prevailing epidemiologic factors to act freely without favoring the natural infection, and (4) by testing certain reactions which may indicate the altered state of immunity in the immunized (antitoxins, humoral antibodies, Schick and Dick tests, tuberculin test, etc.).

The first named procedure was used by Jenner (vaccinia-variola) and was justifiable because variola was quite prevalent. Today this mode of evaluation is probably applicable only in exceptional instances. Similarly, the second method is useful only in professional or occupational groups (laboratory workers) provided the control group is large enough and comparatively uniformly exposed.

Far more effective are the tests in which consideration is given to the interplay of disposition and exposition on the immunized; thus the influence of the immunization on the natural hazard of infections may be evaluated far more accurately than by any other method. When the disposition is maximal and the exposition is great (smallpox), dependable information may be readily obtained. On the other hand, an absence of these premises may render the information secured uncertain. A tendency has thus developed to increase the number of vaccinations in order to be able to express the effect of the immunization by statistical figures. This method has a great many inherent difficulties since the morbidity and mortality for many of the diseases involved in the mass immunizations are subject to great variations. For example, the statistics concerning typhoid vaccination during the War are greatly invalidated since they ignore the faults of the reporting system, the differences between mobile and stationary warfare, the improved condition in the care of the sick, and the inadequate differential diagnosis between typhoid and spotted fever. It is regrettable that these mistakes have not been corrected in connection with evaluation of immunizations against diphtheria and tuberculosis.

The fourth method is for all intent and purposes based on an analogy deduction. In order to be valuable, it is important that the following questions be definitely answered: (1) Are the reactions merely accompanying auxiliary phenomena or (2) are they absolute and essential conditions of the changed state of susceptibility?

In the evaluation of the Schick test, these prerequisites have not been taken into account. It is well known that occasionally Schick-negative individuals may contract diphtheria. As a test, it does not give absolute certainty but merely a high probability for a single case and indicates that an individual has an average resistance against an average infection. Furthermore, it is doubtless questionable to

evaluate an immunization method by a procedure which has not been generally recognized as valid. Therefore, the Schick test can merely be used as an orientation. The antitoxin tests of the blood serum give more information concerning the immunisatoric response than the Schick test. Cases have been reported in which even one antitoxic unit failed to protect against an attack of diphtheria. Furthermore, the antitoxic serum mirror may vary in one and the same individual within a very short time. Severe fatigue or profuse perspiration may reduce or enhance the serum titer. Hamburger and, more recently, Hottinger have noted the interesting fact that children who recovered from diphtheria without the aid of therapeutic injection of antitoxin failed to produce antitoxin. The fact that recovery from diphtheria does not necessarily protect against a second or third attack is usually overlooked, although, according to Zucker's statistic, which embraces only the most susceptible age group, at least 0.9 per cent of the children contract diphtheria a second and 0.13 per cent a third time. Schick and Karasawa even saw a fourth attack.

One may in this connection raise the question: Why does the latent infection and not infrequently the active immunization with toxoids produce far more regularly and more permanently a persistent antitoxin? This important question has not been answered but deserves consideration. At one time the analysis of these observations suggested a desire to revise the theoretic foundations of the active immunization against diphtheria. How this is to be done is not clear. One has, therefore, adhered to the following thought:

The reports on the failures are numerous but in the available statistics the morbidity and the fatality rates of the nonimmunized surpass those of the immunized. The international inquest, which was conducted by the League of Nations, has shown that ten times more nonimmunized contract diphtheria than the immunized, and that the mortality is greatly reduced in some countries even to the zero point.

These critical remarks are not intended to create undue skepticism. Successful immunizations are the crowning achievements of medical research.

However, in the interest of the scientific character of the principles involved and in order to forestall eventual disappointments, it is imperative to check the numerous attempts to discredit valuable and useful methods of immunization by a criticless and planless empirical tendency to propagandize the public for an insufficiently tested procedure of protection which in the natural course of events must lead to mass immunizations and their disappointing consequences.

In order to encourage a general discussion, a few common and then a few less frequently employed methods of immunization may now be briefly presented:

(1) *Smallpox.*—All children should be vaccinated between the sixth and twelfth months of age. This should be repeated whenever the disease is epidemic or in the presence of unusual likelihood of exposure, travel, or contact with cases. The multiple pressure method: 10 to 15 strokes through the drop of virus is generally recognized as the best procedure. In recent years, aside from the well-known glycerinated, vaccinia, vaccine, several newer antigens have been recommended: the chorion-allantoic chick embryo vaccine prepared according to the method of Goodpasture and the lyophile tissue vaccine of Rivers. The latter is administered intracutaneously and is particularly useful when children with skin diseases require vaccination, and when the vaccine has to be shipped under climatic conditions which may readily destroy the potency of the vaccine. The newer preparations are bacteriologically free from micro-organisms other than the elementary bodies of vaccinia. Large comparative series intended to evaluate the antigenic values of the preparations have been carried out by several health departments. The final reports are not yet available.

The type of reactions which must be observed following vaccination, is beautifully illustrated by a chart prepared by the Baltimore Health Department.

Potent antivaccinial sera have been prepared and their use may be considered in the future. For the present, serum treatment of smallpox is in the experimental stage.

At this point, it may be profitable to reflect briefly on the immunity in virus infections. While the knowledge concerning these most intriguing agents of disease was being collected, certain observations assumed the position of facts. For example, it was believed that an active immunity could only be induced by an actual infection, that the resistance was cellular or a tissue immunity, and that the serum antibodies did not react with the virus but as part of the immunity mechanism united with the susceptible cells and protected them against invasion. The increasing number of reports on the immunizing power of heat-killed or formalin-killed virus of herpes, foot-and-mouth disease, vaccinia, psittacosis, and influenza virus cannot be questioned. There is of course the undoubted fact that some of the viruses in a killed state are poor antigens. The absence of serum antibodies in many virus infections does not justify the conclusion that the state of resistance is a true tissue immunity. There is ample evidence to show that if the passive protection against a virus is to be effective, the specific antibody must come into intimate contact with the susceptible cells; it will, therefore, disappear from the circulation or its production will rarely proceed far enough to become demonstrable in the blood stream. True tissue immunity may be operative in the so-called interference phenomenon in yellow fever. The immunity mechanism in poliomyelitis, concerning which there is quite some discussion, may possibly be classed as cellular. From the available data, one could visualize the immunity as follows: The cells of the central nervous system produce their own specific antibodies independent of those found in the circulation. But how does this antibody do its work? Perhaps there is an immunity of the neurons which is independent of the antibody; the insusceptibility is perhaps determined by the persistence of the virus. Since it is not unlikely that the infective agent of poliomyelitis on account of its small particle size is probably a heavy molecular weight protein, this explanation appears reasonable. Equally important in this connection in the question as to whether or not the insusceptibility to infection is dependent on physiologic (endocrines and vitamins) or hereditary factors.

Thus, in all probability, the immunity to animal viruses is only in rare instances of the nature of a tissue immunity. In the vast majority of cases, the antibody is the all-important factor in the immune state. Concerning the mode of action of the neutralizing antibody, it is now strongly suspected that the loose virus-antiserum union, which may be observed by various methods, prepares the virus for phagocytosis and destruction within the cells. Thus the antibody, by uniting with the virus, prevents its penetration in the cells or prepares it for intracellular destruction. But, whichever mechanism it employs, the protection afforded is always relative. Small quantities of virus survive, multiply within cells, and when set free they stimulate antibodies which in turn prevent the level to rise to a stage sufficient to cause clinical symptoms. Thus persistent infections in the immune state or the well-known latency develops. This phenomenon is not only of importance in an explanation of the durable immunity, which so many virus diseases leave behind them, but it plays a prominent role in the epidemiology and has a far-reaching bearing no the immunobiologic methods which are used for the purpose of prophylactic immunization. At this point it may not be out of place to consider the following:

(2) *Rabies Prophylactic Treatment.*—The disease is unduly prevalent, and with increasing frequency decisions have to be made concerning the advisability in recommending the specific prophylactic treatment. During the past fifty years, the original Pasteurian procedure has been modified, primarily to increase the immunity and

secondarily to reduce the complications in form of paralysis or even infection (Högye's method). The fixed virus is subjected either to heat or to the action of chemicals such as carbolic acid or ether. The so-called Semple or phenol-treated vaccine is quite generally used, and although the statistics regularly presented by McKendrick (Bull. Health Organization 6: 17, 1937) would indicate that the killed vaccines give rise to a substantial degree of immunity when given in adequate dosage. There is definite evidence that some preparations on the market are inactive and that, as a whole, they are inferior to vaccines in which the virus is alive but attenuated. On a comparative basis, the etherized vaccines prepared according to Alivisato's method are generally considered superior to the Semple vaccine. Since the immunity mechanism in rabies is by no means understood, it is indeed difficult to evaluate the protection which may be conferred by certain preparations. It is not unlikely that the resistance of the ganglion cells to the virus is independent of the antibodies found in the circulation. For example, a veterinarian, who had been bitten on the thumb by a rabid dog, was thoroughly treated with Semple vaccine, developed neutralizing antibodies in his serum, and yet succumbed to rabies.

While there are several objections to the use of live vaccines in the prophylaxis of most diseases, the fact that the case mortality rate in rabies is so high and the patient is already infected at the time of vaccination does seem to warrant the taking of greater risks. The so-called mixed treatment consisting of etherized vaccine followed by Högye's dilution method or vice versa seems to be justifiable, particularly in deep bites with localization on the head. Those who are frequently brought in contact with the problem of antirabic treatment may profitably consult a recent monograph by Marie J. Van Stockum (New Principles of Antirabic Treatment, Hague, 1935).

(3) *Staphylococcic Infections.*—Based on experimental evidence, it is now believed that pyogenic cocci exert their harmful effect on the tissues by means of toxins, while the resistance is antitoxic in nature. Patients suffering from staphylococcic infections, furunculosis, osteomyelitis, etc., have usually a high antitoxic serum titer. Expressed in so-called international units (1 unit equals amount of specific antitoxic activity contained in 0.5 mg. of dry standard serum; antitoxic activity tested as neutralization of hemolysin, or skin necrotizing effect or death of mouse), it may vary from 1 to 15 units, while in normal persons it is always less than one (0.25 to 0.75 units per cubic centimeter). Highly potent antisera capable of neutralizing the hemolytic, skin-necrosing, lethal, and leucocidic properties have been prepared by inoculation of horses with formalin-treated and later pure toxins. The use of the serum on man is still in an experimental stage, and its usefulness is not established. From a few observations, it appears not unlikely that the antitoxic sera are not capable of neutralizing the intracellular toxins, nor do they protect the leucocytes from the destruction through leucocidins. A serum prepared by treating animals with young staphylococcic cultures contains sensitizing antibodies, which prepare the capsulated cocci for phagocytosis and subsequent leucocidin action. The antibacterial immunity in staphylococcic infections is probably not solely antitoxic.

Staphylococcal toxoid carefully prepared from known strains, which produce no enterotoxic poisons, is used in chronic staphylococcic infections with some success. There is for the present no agreement with regard to dosage and spacing of the injections. Dolman recommends eight weekly injections of 0.05 c.c. progressively increased until 0.5 c.c. is given. Ramon, on the other hand, found that three injections (0.25 c.c., 0.5 c.c., and 2 c.c.) at intervals of from two to three days yielded the highest antitoxin titer on the seventh day. From the evidence at hand, the toxoid is of considerably more value than vaccines, particularly in chronic processes (boils and chronic osteomyelitis). As a whole, the procedure is still in the testing stage and may in time be modified. However, just as in every other method of immunization, perhaps slightly more so in the staphylococcal antitoxin

vaccination, the individual variations in response are quite considerable. Consequently, it is by no means surprising that in small serial observations, the disappointments may overbalance the successes. It is of interest to note that Ramon and his colleagues recommend the combination vaccination with a mixture of staphylococcal toxoid and triple typhoid paratyphoid vaccine.

(4) *Streptococcic Infections.*—Despite a vast amount of research in the field of streptococcic infection, the immunity mechanism is still shrouded in uncertainties. Immunobiologic procedures of various sorts have appeared on the scene like the ebb and flow of the tide. With the advent of sulphanilamide alone or better in combination with convalescent serum, the problem of active immunization has been pushed in the background. In fact, the recent achievements with the erythrogenic toxin as so-called scarlet fever toxoid have not received the attention they deserve. The subject should be discussed, particularly in the light of the reports by Gaylord W. Anderson of the Massachusetts Department of Public Health, who has analyzed a community immunization program involving 14,000 children in orphanages, schools, etc. They had received 0.1, 0.5, and 1 c.c. of toxoid at three weekly intervals. By comparing the attack rates of the immunized and nonimmunized groups, it was consistently noted that the rates were significantly lower among the vaccinated. It is equally noteworthy that the local and general reactions were in no way greater than those observed following diphtheria toxoid.

(5) *Tetanus.*—The tetanus antitoxin acts, not by interfering with the germination of the spores, but by neutralizing the toxin as fast as it is formed. It should be used prophylactically in cases in which there is danger of contamination of a wound with manure, soil, stable dust, etc. The initial dose of 1,500 units (800 to 1,000 units) should be repeated on the fifth day after the initial dose. In fact, third and even fourth injections may be indicated when the wound is very bad. Since the protection wears off in the course of two to three weeks, sensitization with horse serum is undesirable, and sometimes when severe serum reactions accompany the treatment, there is a tendency to reinforce the passive immunity by means of active immunization. The latter procedure is equally advisable in children, who are constantly subject to injuries which may be followed by tetanus. The French Army has pioneered in this field of active immunization. Postinfectional preventive serum therapy is now enhanced by the injection of 1 c.c. of tetanus toxoid about fifteen minutes after the administration of the serum, followed by two injections of 2 c.c. of toxoid at two weekly intervals. Such a treatment raises the antitoxin level of the patient's serum over one quarter unit per c.c., and although at least $\frac{1}{200}$ unit may be demonstrable nine years after the injection of the toxoid, it is advisable to repeat the treatment every time a new injury is acquired. One injection of toxoid seems to push the titer over the minimal requirements. Ramon recommends highly the systematic active immunization of children against tetanus by using the combined diphtheria-tetanus toxoid mixture. Three injections at three-week intervals in dosages of 2 c.c. are used in France. The usual contraindications, malnutrition, and skin diseases equally apply to this procedure. As a rule, the local and general reactions are observed in about 20 per cent of the vaccinated regardless of the dose. Tetanus-toxoid alum precipitated has been used by McBryde and by Goldman in this country. Two injections of 1 c.c. each at an interval of two months, followed by a third injection at the time of injury, permit the practitioner to immunize the allergic child effectively and securely against tetanus.

Whether or not antitoxin is of any value in man when given subsequently to the development of tetanus is a question that has received no definite answer. The evidence merely goes to show that in therapeutic treatment of tetanus, large and repeated doses of serum reduce the mortality. In practice, it seems advisable to administer the serum by the intravenous and intramuscular routes. Patterson, who treated twenty-six consecutive children suffering from tetanus, with only seven

deaths (26 per cent mortality), used the intravenous and intramuscular routes and enormous doses of serum (120,000 to 1,970,000 units). His critics claim that he could have reduced the mortality even further had he adopted the intrathecal administration of one dose of serum (20 to 30 c.c.) by the cisterna magna route as practiced by Yodh in India. The lumbar puncture route is quite generally considered less effective and even harmful.

(6) *Typhoid Fever.*—Typhoid immunization is only recommended for universal application among those who are brought in active contact with the infection, or those who live or travel in regions where the incidence of typhoid fever is great. The heat-killed suspension of typhoid bacilli as vaccine is prepared from carefully chosen strains of potent antigenic make-up. The injection of 0.5, 1.0, and 1.0 c.c. (children 0.25, 0.5, and 0.5) may be given five to fourteen days apart, but equally satisfactory results with less severe reactions are noted when the injections are merely forty-eight hours apart. Vaccination against typhoid fever reduces the case mortality rate and the incidence: for example, in Franklin County, Tennessee, it was 7 per cent in the immunized and 14 per cent in the nonprotected groups. The duration of the immunity is sometimes quite short and it is, therefore, recommended in order to secure continuous protection. One dose should be given each year following the original course of three.

Nonspecific shock therapy with lysed vaccines prepared according to the method of Caronia and even bacteriophage therapy by the intravenous route deserve recognition.

(7) *Tuberculosis.*—It is not within the scope of this general introduction to consider the theoretic views on the immunity in tuberculosis, which have encouraged the search for a practical method of specific acquired immunity. As a whole, the attempts to immunize with dead vaccines or their analogues have been disappointing. Believing that the infection immunity in tuberculosis depends on the persistence of living bacilli, Calmette developed his B.C.G. Although tested on a very large scale, it is very difficult indeed to assess its value. With regard to its use as an immunizing agent for children, at least three questions usually have been answered:

(1) Is the B.C.G. harmless? Aside from the Lübeck catastrophe in which seventy-three out of 251 vaccinated infants died of tuberculosis, and which was almost certainly caused by contamination of the vaccine with a human strain of tubercle bacilli, in no instance could bacteriologic evidence be obtained by competent workers of an increase in virulence or change in type.

(2) Is B.C.G. effective in preventing tuberculosis among vaccinated children? The most reliable and most critically analyzed data show that the death rate is, as a rule, lowered among those children who received the vaccine.

(3) Should the B.C.G. vaccination be used as a public health measure? It is generally admitted that the chances against dying from tuberculosis during the first year of life are about 1,000 to 1. In face of such a low risk, general vaccination by an agent which confers only a moderate protection is out of the question. Finally, both the Scandinavian and American experiences suggest a more effective vaccination by parenteral instead of oral administration of B.C.G. The former has decided disadvantages in causing abscess formation which may ulcerate. Under American conditions, B.C.G. vaccination is not recommended.

(8) *Brucella Infections.*—Clinical infections with Brucella types are relatively rare in childhood, and prophylactic vaccinations are not indicated. Experiments on domesticated animals to immunize with killed vaccines have been disappointing. This is by no means surprising since the Brucella organisms are intracellular parasites, and it is not unlikely that the artificial cultivation may create antigens, which are fundamentally different from those developed during the parasitic existence (T. Smith). Only a true infection may, therefore, produce an immunity. On the other

hand, the possibility must be faced that the susceptible mesenchyme cells and their descendants become immunized during the infection. Consequently, contrary claims, notwithstanding active immunization, require the use of living organisms with the danger in causing latent infections. Therapeutically lysed vaccine administered intravenously may induce shock reactions which, at certain stages of the disease, may hasten recovery. Experience has shown that this form of treatment is valueless during the leucopenic stage, and preparation of the patient by injection of liver preparations is indicated.

(9) *Rickettsia Infection.*—In the western states, the problem of protecting children sent to Rocky Mountain fever areas on vacation has to be faced by the physicians. As a careful critic of the prophylactic vaccination, R. R. Parker has after ten years of experience concluded that the vaccine prepared from comminuted ticks preserved with 2 per cent phenol or a mixture of phenol-formalin is of definite value. Children less than 10 years of age are injected twice with 1 c.c. of the vaccine at weekly intervals. They are better protected than adults, and among them full protection against virus strains of high case fatality seems to be more frequent. It appears that persons who have received vaccines during two or more successive years possess greater resistance than those who have received vaccines only one year. In allergic children the local and general reactions may be quite marked, and intracutaneous test injections are indicated.

(10) *Plague.*—With the recognition of sylvatic plague in many recreational areas and the observations of bubonic plague in children who have handled sick rodents, discussion relative to the needs and merits of prophylactic vaccination has been repeatedly stimulated. The risk of becoming a victim of plague is so small that those familiar with the problem have advised against the use of vaccines even in the most exposed groups. The protective value of heat-killed and avirulent but living vaccines is difficult to assess. The most convincing data collected in the Dutch Indies by Otten strongly favor the use of living avirulent culture vaccines.

Sera have been used in the treatment of plague, and although the evidence that this form of treatment is beneficial is largely circumstantial, it is believed that the patient should have the benefit of this type of therapy. Dried antiplague serum prepared by the Pasteur Institute is available in San Francisco (Hooper Foundation), and will be furnished upon request. The serum should be given in large doses and early in the course of the disease. Surgical interference of the buboes should be carefully avoided.

DISCUSSION

DR. E. B. SHAW (SAN FRANCISCO).—Dr. Meyer always proves to be such a gold mine of information. My principal function on this Round Table has been to bring Dr. Meyer to Del Monte to serve as chairman of this group. I noted that whooping cough was omitted and various phases of the tuberculosis problem were not covered in his paper. There must be many questions in your minds, and the meeting is now open to general discussion.

DR. H. H. PERLMAN (PHILADELPHIA).—Did Dr. Meyer mean that it is impractical to vaccinate newborn infants against smallpox? I understand that the tendency in some clinics at the present time is to vaccinate much earlier than between the sixth and twelfth months of age.

CHAIRMAN MEYER.—It is all right to vaccinate during the first few months of life if one remembers that the degree of immunity conferred is decidedly relative. In some instances the immunity may be very slight so that if a definite exposure occurs later on, even during the last half of the first year, the child must be revaccinated. The reason for stating that the optimum time for vaccination is between the sixth and twelfth months of age is that the child is less likely to be immunologically immature at that time.

DR. A. F. ABT (CHICAGO).—Is it not true that infants in neonatal life react differently in production of humoral immunity than in later life?

CHAIRMAN MEYER.—Yes, and it is the result of many factors, such as heredity, environment, etc.

DR. R. J. DOSTAL (SANTA MONICA).—Since intradermal immunization has been successful in typhoid fever, is it satisfactory in immunizing against scarlet fever?

CHAIRMAN MEYER.—Yes, if the material used is not a formalin preparation, since the latter causes necrosis in many children. When given intradermally the vaccine is administered in ½ c.c. doses in several spots at forty-eight-hour intervals.

DR. ABT.—Do you think that streptococcic toxoid has value?

CHAIRMAN MEYER.—Yes, I do, and it may be of particular value in mass scale.

DR. ABT.—Do you think that each separate type of scarlet fever streptococcus will produce individually different toxoid?

CHAIRMAN MEYER.—No, I do not.

DR. J. W. AMESSE (DENVER).—Is the oral administration of typhoid vaccine to be recommended?

CHAIRMAN MEYER.—Yes, with reservations, if one remembers to prepare the patient before giving the vaccine. Bile should be administered first to increase absorbability. That is rarely done. However, when Dr. Shiga was visiting in San Francisco last year I asked him how he immunizes himself against dysentery, and his answer was most emphatically, "By subcutaneous injections." When large series of individuals have been given the vaccine orally some failures have occurred with later exposures. My friendly advice is "no oral administration of vaccine!"

DR. M. L. BLATT (CHICAGO).—In our prenatal clinic we are determining which mothers and which members of the immediate families are tuberculous so that within the first five days following birth alternate cases are inoculated with B.C.G. The mothers do not know of the two groups and consequently do not know that their babies have not been inoculated if they are in the control group. We are averaging 300 to 500 cases per year. All of the patients are seen monthly for a follow-up study and tuberculin tests and x-ray studies are made from time to time. Having done all this and continued the follow-up for a number of years will you be willing to accept these data when reported?

CHAIRMAN MEYER.—The most critical certainly will say "No!" Even with the best follow-up system there are many obstacles which are difficult to overcome. How long and what kind of exposure will take place? And keep in mind the uncontrollable fluctuations and changes in the social status of these patients. Then there is the danger of the control observations. Who is doing the controlling, the public health nurses, physicians, or who? Remember that the B.C.G. preparation is the easiest part. But the control of the environment is very difficult.

The question of dosage is important. How do we visualize these "massive infections" of which we speak so glibly? Most of the so-called massive infections really represent a cumulative effect of repeated minimal infections. My opinion is that massive infections rarely occur.

Specific acquired immunity to tuberculosis probably does not exist. Sensitization does not mean we are immune. If specific acquired immunity is an important factor our mortality figures would be different. The mortality from tuberculosis in

newborn groups is frightfully high because the exposure occurs in the most susceptible age group. If one cuts off the source of infection immediately following the birth of these babies, even in those families with a bad history of phthisis, the children will be free of infection. A tuberculous family does not necessarily have a high incidence of susceptible offspring. Here on the Pacific Coast, however, we have found that approximately 31 per cent of all freshmen students entering the university have a positive tuberculin reaction. After residence at the university there is a 10 per cent increase each year. How far are we going to go? Remember that man has an inherited disposition to the tubercle bacillus and when exposed 100 per cent, infectious, but not tuberculous, disease will follow. The ability to react to the tuberculous infection is not synonymous with the disposition and is individually quite variable.

DR. BLATT.—This year has seen in Chicago the largest recorded epidemic of measles in recent years. Through the Cook County blood bank we have had available a large amount of bacteriologically tested blood. In the wards we administered pooled adult whole blood to every patient, 10 c.c. to infants, and 20 to 30 c.c. to children more than 1 year of age. Each patient was reinoculated on the eighth day following. Even though a new case of measles occurred about once every week among the new admissions, in spite of rigid precautions to exclude patients in the preeruptive stage, there have been not more than one or two cross-infections. How would you evaluate these observations?

CHAIRMAN MEYER.—I would accept that fully! Your observations provide one more solid pillar on which we are building up the house of measles prophylaxis. Remember though that other antibodies may have been transferred inasmuch as adult whole blood was used.

DR. SHAW.—What is your attitude toward immunization against whooping cough?

CHAIRMAN MEYER.—Because another round table discussion will be devoted entirely to pertussis immunization I purposely did not mention this subject in my paper. But it brings up many questions. Do we know anything but that recovery from pertussis leaves immunity? The mechanism of the immunity we do not know; the *B. pertussis* has a specific organotropism. Is the subcutaneous administration of an antigen imitating the disease process and does it immunize the host cells which are usually disordered by the bacillus? With large doses of carefully killed organisms injected subcutaneously we probably can bring about some degree of immunity of variable and limited duration.

The theory is that during the invasive stage the organism is virulent, but later it changes into a variant which produces the mucoid material causing the whoop. There have been many attempts to devise proper antigens. Sauer has given additional support to various previously reported observations of other workers regarding the effect of injections of Phase I bacilli. His work has demonstrated that large doses of killed organisms are necessary. The idea of toxoid is now being promoted. As yet not enough experience is available and will not be until another five years or so have gone by. It is difficult to evaluate what is really a pertussis infection. And remember that the contagion index of pertussis is between 70 and 80 per cent. The published data are full of errors and discrepancies, but Sauer's vaccine deserves consideration since it has given a striking degree of protection for a limited period of time in a number of serial observations.

DR. SHAW.—Does not the fact that rabies can be prevented by killed rather than by living virus, reopen the entire subject of virus immunity in other diseases such as in poliomyelitis?

CHAIRMAN MEYER.—Killed rabies virus has reduced the postvaccinal complications of paralyses. However, probably phenol reduced the amount of fixed living virus; most of the phenol-treated viruses on the market for the prevention of rabies are valueless in producing immunity. The ether-treated rabies vaccine probably is of the greatest value. Only about 35 per cent of individuals and animals bitten by a rabid animal will develop the disease if unprotected. I am sanguine about the development of an immunizing agent against poliomyelitis.

DR. J. R. LEMMON (AMARILLO, TEX.).—Should antitoxin in epidemic meningitis be given intravenously only?

CHAIRMAN MEYER.—The pathogenesis and variability of the disease is not completely understood. For this reason, some intraspinal serum of high bacteriotropic potency is probably indicated.

DR. DOSTAL.—Has enough work been done to make advisable the use of combined diphtheria and tetanus toxoid?

CHAIRMAN MEYER.—Yes. It should be given in at least two doses with a rather long time interval between injections. If injuries should occur later which ordinarily would make the use of tetanus antitoxin advisable, an injection of tetanus toxoid alone should be given. This avoids the use of horse serum and the dangers of serum reactions and gives more protection.

DR. V. E. STORK (LOS ANGELES).—Is the tetanus toxoid as effective when given with diphtheria toxoid as when given alone?

CHAIRMAN MEYER.—Apparently it is, because of the synergistic effect, the one antigen stimulating the effect of the other. But not all of the tetanus toxoid available commercially at the present time is satisfactory.

DR. W. A. MCGEE (RICHMOND, VA.).—Is it advisable to combine simultaneously two or more different immunizing procedures?

CHAIRMAN MEYER.—One toxoid preparation enhances another toxoid. There are, however, contraindications to combining simultaneously toxoid preparations with other immunizing agents, such as pertussis vaccine, but not with virus procedures, such as smallpox vaccinia vaccination.

DR. A. E. VARDEN (SAN BERNARDINO, CALIF.).—Please discuss some of the differences between alum precipitated toxoid and regular toxoid.

CHAIRMAN MEYER.—The addition of alum to toxoid reduces the absorbability so that the effect is prolonged. Also the alum apparently has the synergistic effect of which I spoke. When the alum preparations were first introduced I defended the use of plain toxoid because I preferred three doses of plain toxoid to one dose of alum precipitated toxoid. Recently, however, fine alum toxoid has been made available with 30 immunizing units per cubic centimeter. But one dose never will produce durable immunity. The first injection produces only basic immunity and further injections are necessary for a high protection. The Danes now are using one dose of alum toxoid and six months later are administering plain undiluted toxoid intranasally. After the child attains school age the intranasal toxoid may be repeated the first of every school year.

DR. FAIRFAX HALL (NEW ROCHELLE, N. Y.).—Is it true that diphtheria incidence has dropped in countries where active immunization is not done routinely as in this country?

CHAIRMAN MEYER.—Yes. That is why we should be exceedingly careful in jumping at conclusions. All we can say is that the mortality has been reduced. We may wake up some fine morning and find that a great many of these children whom we supposedly immunized against diphtheria are actually susceptible to the disease. Biologically we can only expect about 96 per cent protection. And remember that the presence of decent environmental factors is the essential thing in reducing incidence of contagious disease.

Secretaries.

EDWIN J. BARNETT, M.D., *Spokane, Wash.*
NORMAN NIXON, M.D., *Beverly Hills, Calif.*

EIGHTH ANNUAL MEETING OF REGION III OF THE AMERICAN ACADEMY OF PEDIATRICS

The eighth annual meeting of Region III of the American Academy of Pediatrics was held Oct. 27-29, 1938, in Detroit, Mich. The meeting was attended by 180 members, 175 guests, 69 wives accompanying their husbands, and 39 exhibitors—a total registration of 463.

The regional state chairmen met at luncheon on October 28. Dr. A. Graeme Mitchell is chairman of Region III; Dr. Edgar E. Martmer, associate chairman, was chairman of the committee on arrangements.

Six radio interviews broadcast from Detroit stations constituted an important innovation on the program:

The Functions of the American Academy of Pediatrics	Henry F. Helmholz
The Endocrines	A. Graeme Mitchell
The Relation of Mental Hygiene to Pediatrics	Bert I. Beverly
Preventive Pediatrics	Clifford Grulee
Immunization Procedures	John Toomey
Rheumatic Heart Disease	Hugh McCulloch

The following papers were presented:

SESSION I. THE NEONATAL PERIOD

The Significance of Intrauterine Respiration

James L. Wilson, M.D.*

A discussion is given of the status of investigations concerning intrauterine respiration. The expression "intrauterine movements of respiratory muscles" is suggested in preference to "intrauterine respiration" since as yet it is doubtful whether these movements produce a significant pulmonary tidal flow of amniotic fluid.

Cerebral Injury in the Newborn Due to Anoxia at Birth

Frederic Schreiber, M.D., Professor of Clinical Neurological Surgery, Wayne University, Detroit

Asphyxia in the newborn with depression or fatigue of the respiratory center is an important etiological factor in many cases of convulsions, spasticity, and mental retardation in children. These fixed brain lesions, which frequently first manifest themselves a few months after delivery, are secondary to anoxic degenerative cerebral changes.

*All authors are from Detroit except when stated otherwise.

Relation of Maternal Sedation and Anesthesia to Neonatal Asphyxia (Analysis of 5,000 Deliveries)

Warren C. C. Cole, M.D., F.A.A.P., and David C. Kimball, M.D.

Five thousand deliveries at the Woman's Hospital have been analyzed with a view of determining the relationship between sedatives and anesthetics given to the mother and asphyxia in the newborn baby. Scopolomine in any dosage does not seem to increase asphyxia. The barbiturates and similar drugs, while frequently retarding respiration, seldom cause severe asphyxia. Morphine, while seldom given within four hours of delivery, is a definite depressant. Ether or gas anesthesia as used at the Woman's Hospital is not a factor in the production of neonatal asphyxia. By far the majority of severe asphyxias are due to obstetric complications of one type or another. There is evidence that the judicious use of sedatives and anesthetics tends to reduce "birth shock" and the incidence of cerebral injury.

Certain Etiological Factors and the Pathological Lesions in Anoxia

Frank Hartman, M.D., Pathologist, Henry Ford Hospital, Detroit

Anoxia may be due to the operation of one or more of the following physiologic types: the anoxic, anemic, stagnant and histotoxic. In barbiturate poisoning we have early, nearly pure histotoxic anoxia, but later the stagnant type comes into play through the low blood pressure. In acute alcoholism there is again histotoxic anoxia plus the stagnant type, and in one case described, anoxic anoxia resulting from morphine administration and respiratory failure. In the newborn infant histotoxic anoxia results from drugging of the mother, and anoxic anoxia if the delivery is effected under nitrous oxide anesthesia. In concussion, there is stagnant anoxia due to edema and vasodilation with possible histotoxic anoxia as a direct effect of the blow. Shock with falling blood pressure may also be a factor. In fever therapy cerebral anoxia is due to a combination of histotoxic anoxia resulting from heavy sedation in the face of the high temperatures which increase the oxygen demands of cellular metabolism. Stagnant anoxia may also play a role if vascular collapse occurs.

Cerebral Hemorrhage in the Newborn (A Group Treated by Drainage)

John C. Montgomery, M.D., F.A.A.P., and Philip J. Howard, M.D., F.A.A.P.

This is an analysis of 129 cases of intracranial hemorrhage of the newborn, the final outcome of which was known. Eighty-six of these cases were treated by spinal drainage, and 43 were not. Of the 86 children treated, the outcome proved to be 31 normal children, 4 normal mentally but with greater or less neuropathologic findings, 9 idiots, and 42 deaths. A plea is made that tentatively intracranial hemorrhage of the newborn should be treated in the light of a head injury occurring at this age period, and the belief is expressed that it is justifiable to retain a hope that some benefits can be derived from treatment and that only by making such attempts can a final solution of this difficult question be acquired.

Erythroblastosis of the Newborn

Thomas B. Cooley, M.D., F.A.A.P.

There are discussed the distinction of this condition from malignant jaundice due to sepsis, the frequency and importance of the condition, the desirability of its recognition by obstetricians, the relation to anemia of newborn, and possible theories of etiology and pathogenesis.

SESSION II. NUTRITION AND METABOLISM

Relation of Growth and Skeletal Maturity to the Mineral Balances of Children

Icie G. Macy, Ph.D.

A longitudinal study extending over six continuous months showed that ten children, carefully selected as representative of average healthy American children, varied greatly in their calcium storage and accumulation in spite of a three-month prefeeding period and an adequate and fairly constant calcium intake. The range of the individual variations narrowed each successive month. The variations in calcium retention are related to previous state of nutrition, and bone development and growth.

Biological Time Patterns in Gastrointestinal Motility of Children

Lawrence Reynolds, M.D., Associate Professor of Clinical Roentgenology, Wayne University, Detroit

The individual variation in the gastrointestinal motility of children and the variation in motility produced by different types of meals is indicated by thirty-two series of roentgenograms consisting of 280 films of eight children living under standardized conditions of diet and environment. Meals of barium-and-water, -milk, -glucose, -cream, and -meat, were given upon different days and followed by means of roentgenograms taken at short intervals for several hours after ingestion. Films were also exposed at twenty-four and forty-eight-hour intervals after administration of the meals.

The biologic time patterns shown by the different series of roentgenograms are compared: for the stomach alone, for the entire gastrointestinal tract at the end of twenty-four hours, and for the entire tract after forty-eight hours.

Metabolism of Citric Acid in Infancy

A. H. Smith, Ph.D., Professor of Physiological Chemistry, Wayne University, Detroit

Thirteen infants (3 to 14 months of age) metabolized the citric acid occurring naturally in the diet to the extent of 79.5 to 96 per cent. In general, more citric acid was excreted in the urine than in the feces, the renal elimination amounting to 3.9 to 13.3 per cent of the intake.

Serum Phosphatase in Relation to Vitamin D

Donald J. Barnes, M.D., F.A.A.P.

Measurements were made of vitamin D effects upon the serum phosphatase in infants, using different vitamin D sources. The studies include attempts to establish normals for serum phosphatase during the first year of life, effects upon the serum phosphatase of different dosage levels of vitamin D in patients who show rachitic tendencies, and correlations of these with calcium and phosphorus storage.

Vitamin C Requirements of Artificially Fed Infants

Brenton M. Hamil, M.D.

Four hundred and twenty-seven (427) infants were observed for data relative to the "plane of health" through the first year of life. On a controlled dietary containing 10 mg. of ascorbic acid (200 international units) daily, evidence of

mild (preclinical) scurvy according to the criteria of Park and co-workers was observed to develop in 20 cases (4.68 per cent). An analysis of these data for this factor is presented. The individual requirement is variable and is influenced by prenatal as well as postnatal factors. Scurvy is apparently a definite pathologic entity but does not become evident or retard development until the absence of the specific physiologic functions of the vitamin is manifest.

Relation of Craniotabes to Diet and Growth

Marsh Poole, M.D., F.A.A.P.

In four hundred and twenty-seven infants who were cared for in the clinic of the Children's Fund of Michigan and the Children's Hospital throughout the years 1933 to 1936, craniotabes was found in a considerable percentage. A control group of 1933-1934 received no vitamin D except that naturally contained in the diet. In this mixed group of colored and white infants 46 per cent had moderate or severe rickets, and 60 per cent showed softening of the cranial bones at some time during the year. A superior group cared for in 1935-1936 who had vegetable soup in their diet from the first clinic visit and received cod liver oil throughout, developed the same percentage of craniotabes, but there was only 5 per cent of slight rickets as shown by roentgenograms. Analysis of the records of other groups showed practically the same percentage of softening in the skulls of colored and white infants. The highest percentage of craniotabes was found among premature infants and twins. Of twenty-one babies diagnosed as having mild scurvy by x-ray, nineteen showed softening of some degree.

The majority of babies with moderate or severe craniotabes had severe or repeated respiratory infections, eczema, vomiting, parenteral diarrhea, loss of appetite, or some other disturbance which may have accounted for the inability to deposit sufficient calcium in the rapidly growing cranial bones.

Metabolic Observations on a Child With Essential Hyperlipemia

Samuel Bernstein, M.D.

A short metabolic study was made of a six-year-old boy with a marked, chronic idiopathic lipemia. The following data were determined while the boy was on a low and then on a high fat diet: nitrogen balance and distribution in the urine, lipin distribution in the blood and stool, and mineral balance. In addition, his respiratory quotient and specific dynamic response to fat and carbohydrate were studied.

Session III. Endocrine

Metabolic Effects of Growth and Thyrotropic Hormones Administered With and Without Iodine

O. H. Gaebler, M.D., and Paul Bartlett

In experiments on dogs, daily records were kept of the weight, water intake, urine volume, the excretion of total nitrogen, creatinine, and creatine, and the basal metabolism. Addition of 1 c.c. of Lugol's solution to the daily ration did not significantly alter the nitrogen storage or calorigenic effect resulting from single injections of the growth preparation. Marked storage of creatine accompanied the storage of nitrogen. Single injections of thyrotropic hormone produced just detectable calorigenic effects, but produced a marked creatinuria which was not prevented by administration of iodine, and differed in this respect from the

creatinuria of human hyperthyroidism. The animals become refractive to the action of the thyrotropic hormone on creatinuria after as few as three small injections at ten-day intervals.

Relation of Diet to the Experimental Production of Goiter

G. R. Sharpless, Ph.D.

In five to seven weeks the thyroid gland is enlarged to four times normal in rats fed a diet of raw soy bean flour, yeast, butterfat, sugar, and salts. Iodine will prevent the enlargement, but the minimum requirement is greater than that for rats fed on other diets. Treating the flour by prolonged heating or extracting with solvents reduces its goiterogenic activity even though the iodine content of the diet may be reduced.

Effect of Thyroid on Nitrogen and Calcium in the Growth Period

John W. Maroney, M.D., F.A.A.P., and J. A. Johnston, M.D., F.A.A.P.

Continuous calcium and nitrogen balances with concurrent basal metabolic determinations were made on a cretin to whom thyroid was administered and an adolescent with hyperthyroidism whose gland was removed. Retention of both calcium and nitrogen was increased with the administration of thyroid. The child with hyperthyroidism showed a negative calcium balance which became positive with thyroidectomy. However, when the basal metabolic rate fell to –20 per cent following the removal of both lobes, a slightly positive calcium balance became definitely more positive with the administration of thyroid. The improvement was referable to a diminished stool loss. The negative balance in the hyperthyroid state was associated with a high urinary output. A similar anabolic effect was noted in the case of nitrogen.

A Continuous Calcium and Nitrogen Balance in a Case of Legg-Perthes' Disease Treated With Growth Hormone and Thyroid

C. L. Mitchell, M.D., and J. A. Johnston, M.D., F.A.A.P.

A continuous calcium and nitrogen balance for sixty-six days with concurrent basal metabolism determinations was obtained on a boy with Legg-Perthes' disease. The calcium balance was negative on an average intake, was not appreciably changed by growth hormone, but was made definitely positive by thyroid. The basal metabolism was low. The intercurrence of an acute throat infection rendered the balance again negative, but, following its subsidence, it became positive again with thyroid. Clinically the patient improved rapidly.

Continuous Nitrogen and Calcium Balances Throughout the Periods Just Preceding and Following the Menarche

J. A. Johnston, M.D., F.A.A.P.

Continuous nitrogen and calcium determinations before and after the menarche show a fall in the retention of these substances following the menarche. The basal metabolism throughout this period was irregular, but was relatively elevated before and depressed following the first menstrual period; the retentions of calcium and nitrogen were, accordingly, higher with the more elevated rates and lower with the depressed rates.

SESSION IV. CLINICAL TOPICS

Comparison of Specific and Nonspecific Serum Treatment in Scarlet Fever

Donald C. Young, M.D., Medical Director, Communicable Disease Division, Herman Kiefer Hospital, Detroit

The results of the treatment of alternate cases of moderately severe scarlet fever with scarlet fever antitoxin, scarlet fever convalescent serum, and a nonspecific horse serum are given. The trial period covered one epidemic year. Comparability of the several groups was determined by statistical methods and satisfied the requirements of random selection. No significant difference could be demonstrated in the results obtained with convalescent serum and with specific scarlet fever antitoxin, but little or no value could be demonstrated to result from nonspecific serum.

The Common Ground of Pediatrics and Orthodontics

Samuel J. Lewis, D.D.S.

Like the pediatrician, the orthodontist is dealing with an unfinished product—the child. The dentition of the child is an organ in transition and must be appraised only in accordance with the stage of development attained at the time it is observed. Orthodontic treatment, then, should be instituted when it will do the most good and be of undoubted benefit to the child.

Sulfanilamide in the Treatment of Gonorrheal Ophthalmia

Merrill Michels, M.D.

We have observed a reduction of hospitalization from 28.5 days for a control series of thirty-two patients with gonorrheal ophthalmia to 5.8 days for a series of fifteen patients similarly treated but with the addition of sulfanilamide. Sulfanilamide is warranted in the treatment of gonorrheal ophthalmia because: (1) it reduces the length of hospitalization, (2) its ease of administration, (3) the lack of complications, (4) the rapid improvement noted, and (5) general increase in comfort of patient.

The Use of Small Intestinal Decompression in the Treatment of Intestinal Obstruction

Charles G. Johnston, M.D., Professor of Surgery, Wayne University, Detroit

Intubation of the small intestine with suction drainage has been used in a sufficient number of cases of ileus of the dynamic and adynamic types to determine its advantages and disadvantages. A brief description of the method and a discussion of the results of its use are presented.

The Endogenous Reinfection Type of Tuberculosis in Childhood With Particular Reference to the Girl at Puberty

Bruce Douglas, M.D., Controller of Tuberculosis, Department of Health, Detroit, and J. A. Johnston, M.D., F.A.A.P.

A study of over 900 children over a period of ten years, many of whom were originally familial contacts to tuberculosis, indicated a larger number of re-infection type cases of tuberculosis developing than would be expected ordinarily in spite of the fact that these children were removed to foster homes free from tuberculosis. Girls developed active tuberculosis at puberty under these circum-

stances much more frequently than boys, suggesting that certain physiologic changes allow the already present infection to become active.

Phlyctenular Conjunctivitis: Course and Treatment

Philip J. Howard, M.D., F.A.A.P.

A series of 18 children with phlyctenular conjunctivitis was followed. The most satisfactory treatment consisted of desensitization with tuberculin after first carefully determining the threshold of reactivity by doing skin tests with serial dilutions. The most minute amount of intradermally administered old tuberculin to which the child would react was taken as the threshold, and desensitization was carried out by subcutaneous injections at five-day intervals, starting with an amount smaller than the lowest skin sensitivity dose. As desensitization progressed, the eye lesion healed.

Undulant Fever: Diagnostic and Therapeutic Measures

John Sander, M.D., F.A.A.P., Lansing, Mich.

A résumé of the signs and symptoms of juvenile brucellosis, with a critical analysis of the diagnostic and therapeutic measures currently available.

Sulfanilamide Therapy in Erysipelas

Harry T. Mernagh, M.D.

Approximately one hundred cases of erysipelas of the face, body, and extremities were treated with sulfanilamide. These are grossly compared with the results of treatment covering an experience of five years just prior to the introduction of sulfanilamide. The value of this drug in the treatment of erysipelas following such a comparison appears to be demonstrated.

Jaundice: An Epidemiological and Bacteriological Study of a Small Outbreak in Detroit

Joseph G. Molner, M.D., Director, School Health Service, Department of Health, Detroit

The study reported of 185 cases of jaundice is presented with a discussion of clinical and bacteriologic findings and an hypothesis of the transmission of the condition.

Diaphragmatic Hernia in Children

John B. Hartzell, M.D.

An analysis was made of 68 cases of diaphragmatic hernia in children under 10 years of age, treated by operation. Criteria for diagnosis, methods of treatment, and mortality statistics are presented.

Session V. Papers From the Department of Pediatrics, University of Michigan

Acidosis Associated With Sulfanilamide Administration

Harry A. Towsley, M.D., and John J. Engelfried, M.D., Ann Arbor, Mich.

A study was made of the relationship of the carbon-dioxide combining power of the plasma and the blood concentration of sulfanilamide. Results showed a definite and sometimes very marked decrease in the CO_2 combining power of the plasma during the administration of the drug. For the most part a compensated acidosis was produced, and in a few an uncompensated acidosis, which is relieved by the administration of alkali.

The First Heart Beats and the Beginning of the Circulation of Blood as Shown by Micromoving Pictures of Living Embryos

Bradley M. Patten, M.D., Professor of Anatomy, University of Michigan, Ann Arbor, Mich.

The adaptation of tissue culture methods to handling entire embryos of laboratory animals in specially constructed glass chambers is beginning to be developed to a point which makes possible continued observations of developmental phenomena in living material. This paper deals with the application of such methods to the study of the initiation of cardiac contraction and the first movement of blood corpuscles in chick embryos. Microcinematography has been used as a method of recording and demonstrating these events and some of the significant changes that occur in the action of the embryonic heart during its conversion from a primitive tubular structure into the chambered organ characteristic of older embryos and adults.

Our Clinical Experience With the Treatment of Thirty Cases of Hirschsprung's Disease (Megacolon)

John L. Law, M.D., Ann Arbor, Mich.

A discussion is given of thirty cases of megacolon with reference to etiology, pathology and treatment. Highly encouraging results have followed the use of mecholin in the last several years which are comparable with those of sympathectomy.

The Role of the Pediatrician in Mental Hygiene

Paul H. Jordan, M.D., Ann Arbor, Mich.

It is now an accepted fact that most personality and behavior disorders of adults have their beginnings in unwholesome reactions to childhood experiences; therefore, the pediatrician, because of his particular field in medicine, is in a strategic position from the standpoint of mental hygiene. Emotional problems in children may arise associated with, or entirely separate from, actual physical disease and should be recognized and the proper treatment instituted at the earliest possible moment. While the pediatrician can and should handle many of the less complex disorders of children himself, in more serious cases, because of their complexity, he should seek the services of certain technical specialists, the child psychiatrist, the clinical psychologist, and the psychiatric social worker, just as he now makes use of the contributions of the roentgenologist, the otolaryngologist, and other medical specialists in the case of obscure physical disease.

A Mechanical Presentation of the Effects and Interrelationships of the Human Female Hormones of Reproduction During the Menstrual Cycle and Pregnancy

Wayne L. Whitaker, M.D., Ann Arbor, Mich.

An apparatus has been constructed in an attempt to illustrate graphically the cyclically changing amounts of various hormones of reproduction present in the body during the several stages of the menstrual cycle and pregnancy. The hormones considered are the follicle-stimulating, luteinizing, and lactogenic factors of the anterior pituitary, folliculin, and progestin from the ovary, and the pregnancy estrogen and anterior pituitary-like substances probably produced by the placenta. Cause and effect relationships between the hormones as well as endocrine influence on the reproductive organs are suggested.

Academy News

Region I of the Academy held its annual meeting on Friday, November 11, and Saturday, November 12, at Rochester, N. Y.

Region II held its annual meeting on Wednesday, November 16, at Oklahoma City, Okla. This meeting was held at the time of the Southern Medical Association.

Region IV will hold its next annual meeting on April 27, 28, 29, 1939, at Oakland, Calif. Dr. Clifford Sweet, state chairman for northern California, will be in charge of the scientific program.

At the meeting of Region III of the Academy in Detroit, the following resolution was adopted:

"Within the past month Dr. Russell Sturgis Rowland, of Detroit, has passed away. Dr. Rowland was an early member of the American Academy of Pediatrics and vitally interested in its inception and development. He was not only a notable exponent of the best in pediatrics as a practitioner but contributed importantly as well by his investigations to its scientific progress. In view of the sad loss occasioned by Dr. Rowland's death,

"BE IT RESOLVED that this body expresses its grief in his demise and extends to Mrs. Rowland and family its profound regret and sympathy."

News and Notes

The **American Board of Pediatrics** will hold examinations during 1939 as follows:

April 26, 1939, in New York, N. Y. Appointments for this examination must be made before Dec. 26, 1938.

May 16, 1939, in St. Louis, Mo., during the meeting of the American Medical Association. Appointments for this examination must be made before Jan. 16, 1939.

November 14 and 15, 1939, in Cincinnati, Ohio, preceding the annual meeting of the American Academy of Pediatrics. Appointments for this examination must be made before July 14, 1939.

The **Pediatric Section** of the American Medical Association has had Hotel Chase assigned as headquarters for the St. Louis meeting May 15-19, 1939. It is suggested that those expecting to attend the meeting make reservations early. Rates: Single from $3.00; double from $4.00; and twin bed double from $5.00. For advance reservations address John Reinhardt, A. M. A. Housing Bureau, 910 Syndicate Trust Building, St. Louis, Mo., since all reservations must clear through this agency.

Announcement is made by Dr. A. Graeme Mitchell, director of The **Children's Hospital Research Foundation**, Cincinnati, and Dr. Glenn E. Cullen, director of laboratories, that upon authorization of the board of trustees a scientific advisory council has been appointed. This consists of:

Dr. O. T. Avery, member of the Hospital of the Rockefeller Institute for Medical Research.

Dr. Ernest Goodpasture, professor of pathology, Vanderbilt University School of Medicine.

Dr. A. Baird Hastings, professor of biological chemistry, Harvard University Medical School.

Dr. A. N. Richards, professor of pharmacology, University of Pennsylvania School of Medicine.

The second meeting of this council was held in Cincinnati on Sept. 28 and 29, 1938.

The Children's Hospital Research Foundation was created in 1929 through the generosity of Mr. William Cooper Procter. Its facilities include its own laboratory building and affiliations with the Children's Hospital of Cincinnati, the Pediatric Department and the Contagious Disease Pavilions of the Cincinnati General Hospital, the Children's Convalescent Home, the Babies' Milk Fund Association, and the Ohio Soldiers' and Sailors' Orphans' Home at Xenia, Ohio. The Children's Hospital and its Research Foundation are affiliated by agreement with the University of Cincinnati, the professor of pediatrics in the University of Cincinnati being the director of the medical service and the director of the Foundation. Approximately one hundred and fifty publications have appeared from the Research Foundation. Present plans contemplate additions to the staff and certain new lines of investigation.

Dr. Haskell Talamo, Worcester, Mass., died July 10, 1938, of subacute bacterial endocarditis. Dr. Talamo was an instructor in the Department of Pediatrics of Tufts Medical College.

Dr. Rolf R. Struthers has been appointed professor of pediatrics at McGill University and physician-in-chief at the Children's Memorial Hospital in Montreal to succeed Dr. H. B. Cushing, who becomes emeritus professor of pediatrics and honorary physician-in-chief, respectively.

Dr. C. A. Earle, of Des Plaines, Ill., died October 29.

The following have been certified by the **American Board of Pediatrics** since the last report.

Dr. I. Pat Bronstein, Chicago, Ill.
Dr. Daniel Budson, Detroit, Mich.
Dr. Vernon Richard DeYoung, Chicago, Ill.
Dr. George L. Drennan, Jacksonville, Ill.
Dr. Joseph A. Gilmartin, Pittsburgh, Pa.
Dr. Brenton M. Hamil, Detroit, Mich.
Dr. Samuel J. Hoffman, Chicago, Ill.
Dr. John L. Law, Ann Arbor, Mich.
Dr. Benjamin M. Levin, Chicago, Ill.
Dr. George Calvert Malley, Zanesville, Ohio
Dr. Charles Miles McKinlay, Lexington, Ky.
Dr. Frederick William Munro, Detroit, Mich.
Dr. Samuel J. Nichamin, Detroit, Mich.
Dr. Mila I. Pierce, Evanston, Ill.
Dr. Joseph Nathan Rappaport, Evanston, Ill.
Dr. Walter J. Siemsen, Chicago, Ill.
Dr. Ralph Spaeth, Chicago, Ill.
Dr. M. I. Vinnecour, Chicago, Ill.
Dr. Robert Breckinridge Warfield, Lexington, Ky.
Dr. Dwight Addison Weir, Mansfield, Ohio
Dr. Lawrence J. Wilhelmi, Joliet, Ill.
Dr. James L. Wilson, Detroit, Mich.

Book Reviews

Babies Are Human Beings. C. Anderson Aldrich and Mary M. Aldrich, New York, 1938, The Macmillan Company, pp. 128, Price $1.75.

This little volume by Dr. Aldrich and his wife may be regarded in a certain sense as marking a real epoch in pediatric literature. It is the first successful attempt to put modern scientific knowledge of the growth and development of the infant into an understandable form for parents. On this basis a method of approach is offered to an understanding of just what the young growing organism is doing and why he is doing it. It must not be confused with the scores of books on the care of the baby with which the market is flooded. While the authors have drawn freely on the recent work of students of development, they have contributed an invaluable selection of material based on Dr. Aldrich's experience and knowledge of what parents need.

An idea of the method of treatment of the subject may be gathered from the chapter headings: "Beginnings"; "The Baby's Dilemma"—the conflict between normal growth processes and the environment in which he finds himself; "The World Comes to the Baby"—perception through the development of the special senses; "The Baby Responds to the World"—motor development; "Babies Are Different"—the matter of individual variation; "The Baby's Way of Sleeping"; "Eating"; and "Eliminating"; "Among the Do's and Don't's"—all too brief; and "Implications for Older Children."

While written primarily for the parent, the book presents in an interesting nontechnical way so much factual data unknown to many practitioners of medicine that it has a real value for the physician. The reviewer has encountered one teacher of pediatrics who has already put it on the reading list for his medical students. It is, moreover, a real pleasure to run across a book by a physician (not forgetting the coauthor) which is so well written from a purely literary standpoint. The authors are to be congratulated on having made a real contribution.

Internships and Residencies. Report by The New York Committee on the Study of Hospital Internships and Residencies. New York, 1938, The Commonwealth Fund, Price $2.50.

This report is an outstanding study of the complex problem of hospital internships and residencies. In recent years there has been an increasing realization that the hospital services are a part of and must be integrated with the medical education program. In fact, the internship is regarded by many educators as a part of the undergraduate training of the physician. The newly formed specialty boards to a large extent have passed the training of the "specialist" back to the hospital residencies. If the problem of preparing the physician for practice necessitates, as it apparently does, an internship, and a residency is the sine qua non for the specialist of the future, it is time the various types and kinds of house services, the methods of appointment, the character of the training received, and similar subjects be approached from the general viewpoint of education rather than the viewpoint of the demands and needs of the institution.

Although this report is based on a study of hospitals in New York City, we feel its findings apply with a few minor exceptions to the conditions existing in any large city. New York differs only in two particulars. One is that the five local

medical colleges can and do furnish less than half of the annual appointments. The balance come from seventy-two American and Canadian schools in which the training is similar, and from thirty-one foreign institutions, many of which have uncertain standards. Thus the selection of the house staff constitutes more of a problem than in other cities. In the work of the New York intern the "ambulance service" forms a constantly increasing chore, disrupting the education of the house staff to an extent not found in many other cities. With these two exceptions the study in all probability reflects the situation as it exists in other large cities and hence has a general rather than a local importance.

The study was made by a joint committee of the five local medical schools and the New York Academy of Medicine, with Dr. Jean A. Curran as executive secretary. It is excellently written, and the material presented with care and understanding. Of the 182 hospitals in New York, 77 are approved by the Council on Medical Education of the American Medical Association. All of these were surveyed, and in addition 20 of the 105 nonapproved hospitals were studied as a sample for comparison. In the approved hospitals, which form the basis of the report, there were 1,760 approved positions. Of the 1,245 internships, 902 (72 per cent) are rotating. The services to which the intern is assigned on a rotating service show infinite variation. While the average is from five to seven services, in two hospitals the interns served on fourteen different services. Although the majority of rotating services are two years in length, the "block," or period of time, devoted to the important services was too short in the opinion of the committee in almost every instance. There were 545 residencies in the approved hospitals, of which 35 were pediatric.

Much of the report is necessarily statistical, but there is an excellent discussion of such topics as the relation of the internship to practice, libraries and their use, the preparation of the intern for his work, the training of the intern, health and housing, method of appointment, and the like.

The chief criticism made of the pediatric training is the short time allowed for this service in the rotating internship. The committee feels that three months of pediatric service should be included in the rotating internship. In the 43 hospitals with rotating internships of eighteen months or more, 35 have pediatric assignments of less than three months. "The relationship noted between the short assignments and the quality of work was more striking in pediatrics than on any other service." There are 35 pediatric residencies available in the New York hospitals. In 24 of these the training received was estimated as good, in 10, fair, and in 1, doubtful. Sixteen of the men holding these 35 appointments plan to enter the field as a specialty.

This report should be required reading for hospital administrators, chiefs of staff, and members of intern committees, for it is upon these groups that the fate of the house officer depends. The New York committee has rendered a valuable service to colleagues throughout the country.

B. S. V.

Erratum

In the article, "Serum Treatment of Pneumonia in Childhood," by Rosa Lee Nemir, M.D., New York, N. Y., which appeared in the August issue of the JOURNAL, line 8 on page 221 should read:

"the swab. Occasionally good material may be found on the back of the"
instead of
"the Neufeld (quellung) reaction as adapted originally by Sabin[5a] for"

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A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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Published by THE C. V. MOSBY COMPANY, 3523-25 Pine Blvd., Saint Louis, U.S.A.

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